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(54) **Laulimalide-derivates, their use and process for the production of laulimalide and laulimalide-derivates**

(57) Described are laulimalide-derivatives, their use and a process for the production of laulimalide (Fijanolid B; structure see formula I, in which X and X₁ has the meaning of oxygene, R₁ has the meaning of α -methyl, Z₁ has the meaning of a (E)-double bond, Z₂ has

the meaning of an β -epoxide and Z₃ has the meaning of a (Z)-double bond) and its derivatives. The invention further relates to the intermediates used for the production of laulimalide and laulimalide-derivatives.

Description

[0001] The invention relates to laulimalide-derivatives, their use, and process for the production of laulimalide (Fijanolid B; structure see formula I, in which X and X₁ has the meaning of oxygene, R₁ has the meaning of α -methyl, Z₁ has the meaning of a (E)-double bond, Z₂ has the meaning of an β -epoxide and Z₃ has the meaning of a (Z)-double bond) and its derivatives. The invention further relates to the intermediates used for the production of laulimalide and laulimalide-derivatives.

[0002] The interest in a total synthesis of natural products, such as laulimalide has been kindled by the striking success of paclitaxel as a novel drug against previously incurable tumors. However, in view of the manifold problems met during the clinical application of paclitaxel, a great deal of effort has been focused on potential successors with the same mode of microtubule stabilizing antitumor action, however, with better bioavailability and higher activity against multidrug resistant tumor cells. Among recent advances have been epothilone B and derivatives, discodermolide and eleutherobin. Quite recently, it has been discovered that laulimalide, a metabolite from various marine sponges, also shows microtubule stabilization in eukaryotic cells, however, with better bioavailability and high antitumor activity against multidrug resistant cells lines. To date, only one total synthesis of laulimalide has been published along with several approaches to major fragments (Synthesis of Fragments:

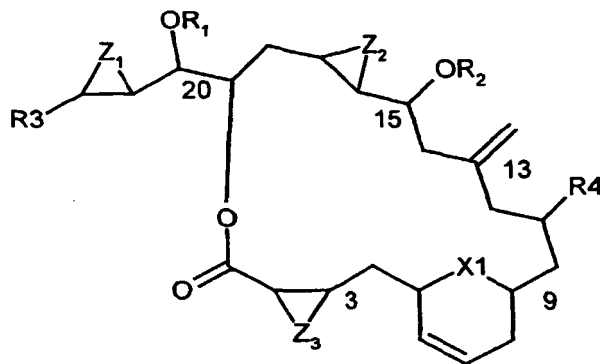
- (a) Shimizu, A.; Nishiyama, S. *Tetrahedron Lett.* **1997**, *38*, 6011-6014.
- (b) Shimizu, A.; Nishiyama, S. *Synlett* **1998**, 1209-1210) (c) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1997**, *38*, 2427-2430. (d) Ghost, A. K.; Wong, Y. *Tetrahedron Lett.* **2000**, *41*, 2319-2322.
- (e) Mulzer, J.; Hanbauer, M. *Tetrahedron Lett.* **2000**, *41*, 33-36.
- (f) Dorling, E. K.; Öhler, E.; Mulzer, J. *Tetrahedron Lett.* **2000**, *41*, 6323-6326.
- (g) Dorling, E. K.; Öhler, E.; Mantoulidis, A.; Mulzer, J. *Synlett* **2001**, 1105-1108.
- (h) Nadolski, G. T.; Davidson, B. S. *Tetrahedron Lett.* **2001** *42*, 797-800.
- (i) Messenger, B. T.; Davidson, B. S. *Tetrahedron Lett.* **2001** *42*, 801-804.
- (j) Paterson, I.; Savi, C. D.; Tudge, M. *Org. Lett.* **2001**, *3*, 213-216.

[0003] Total synthesis: Ghost, A. K.; Wong, Y. J. *Am. Chem. Soc.* **2000**, *122*, 11027-11028. *Tetrahedron Lett.* **2001**, *42*, 3399-3402).

[0004] There is a high demand for further active compounds which can be used for different diseases, and which show a reasonable bioavailability together with antitumor activity. Further, there is a high demand for an effective process for the production of said natural product compounds.

[0005] The disadvantages of the known process is the lower yield combined with the huge amount of process steps.

[0006] It has now been found that laulimalid derivatives of general formula I

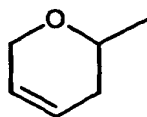


(I),

in which

R¹ and R² independently from each other have the meaning of hydrogen, α -alkyl, β -alkyl, methylmethylether, alkyl

- optionally substituted with hydroxy, paramethoxybenzyl, benzyl, or a protecting group,
 R³ has the meaning of a five or six membered, optionally substituted aryl or heteroaryl ring, or a five or six membered optionally substituted and optionally partially saturated cycloalkyl ring, which can be interrupted by oxygen, sulphur or the group =NR⁵,
 5 R⁴ has the meaning of α -alkyl, β -alkyl, aryl or trifluoromethyl,
 X₁ has the meaning of oxygen, sulphur or the group =NR⁵, in which
 R⁵ has the meaning of hydrogen, alkyl, cycloalkyl or aryl,
 Z₁ has the meaning of a (Z)- or (E)-double bond, triple bond, or has the meaning of oxygen, sulphur or the group -CH₂-, -CH₂-CH₂-, =C(OH)₂, =C(halogen)(OH), =C(OH)NR⁶ or =NR⁷,
 10 Z₂ has the meaning of a (Z)- or (E)-double bond, triple bond, or has the meaning of oxygen (α - or β -epoxide), sulphur or the group -CH₂-, -CH₂-CH₂-, =C(OH)₂, =C(halogene)(OH), =C(OH)NR⁶ or =NR⁷,
 Z₃ has the meaning of a (Z) or (E)-double bond,
 R⁶ has the meaning of alkyl, cycloalkyl or aryl, and
 R⁷ has the meaning of hydrogen, alkyl, cycloalkyl or aryl, and the optical isomers and salts thereof, except
 15 of those compounds in which R³ stands for the cycloalkyl ring



20 and X₁ has the meaning of oxygen, R¹ has the meaning of α -methyl, Z₁ has the meaning of a (E)-double bond, Z₂ has the meaning of β -epoxide if Z₃ has the meaning of a (Z)-double bond, overcome the known disadvantages.

[0007] The inventive compounds can be used as medicament for the treatment of cancer, such as solide tumors and Leukemia, autoimmune diseases, such as psoriasis, alopezia and multiple sklerose, chemotherapeutically induced alopezia and mukositis, cardiovascular diseases, such as stenosis, arteriosclerosis and restenosis, infectious diseases caused by unicellulare parasites, such as trypanosoma, toxoplasma or plasmodium, or nephrological diseases caused by fungi, such as glomerulonephritis, chronical neurodegenerative diseases, such as Huntington's disease, amyotropical lateral sclerose, Parkinson disease, AIDS dementia and Alzheimer's diseases, acute neurodegenerative disease, such as mia of the brain and neurotraumata, virale infekions, such as wie z. B. Cytomegalus-infekiones, herpes, hepatitis B and C, and HIV diseases.

[0008] Thus, the use of the inventive compounds is also claimed matter.

[0009] For the use of the compounds of general formula I as medicament, compounds are brought into a pharmaceutical formulation, which beside the active inventive compound further comprises organic or inorganic inert carrier materials, such as water, gelatin, gum Arabic, lactose, starch, magnesia stearate, talc, vegetable oils, polyethylene glycols, etc.

Said formulations can be used for enteral or parenteral applications.

These pharmaceutical formulations can be applied in solid form, such as tablets, pills, suppositories, capsules; or in fluid form, such as solutions, suspensions, or emulsions.

If necessary, these formulations further comprise additives, such as preservatives, stabilizers, or emulgators; and salts for the change of the osmotic pressure or as buffer.

For parenteral application special injectable solutions or suspensions, especially liquid solutions of the active compound in polyhydroxy ethoxylated castor-oil are suitable.

[0010] As carrier systems it is also possible to use salts, such as gall acid, or plant or animal phospholipids, or a mixture thereof, as well as liposomes or compartments thereof.

50 [0011] For an oral application, especially tablets, pills or capsules can be used, which comprise talcum, and/ or hydrocarbon carriers or binders, such as lactose, maize or potatoe starch.

The application is also possible as fluid formulation, such as juice, added with sweeteners, or if necessary with one or two artificials.

[0012] The dosis of the active ingredients can vary, depending on the way of application, age and weight of the patient, as well as difficulties with respect to hat disease, and other problems.

[0013] The daily dosis is 0,5-1000 mg, especially 50-200 mg. The dosis can be applied as single dosis, or separated as two or more daily dosages.

The formulations and appliable forms of the inventive compounds described above, are also claimed matter of the

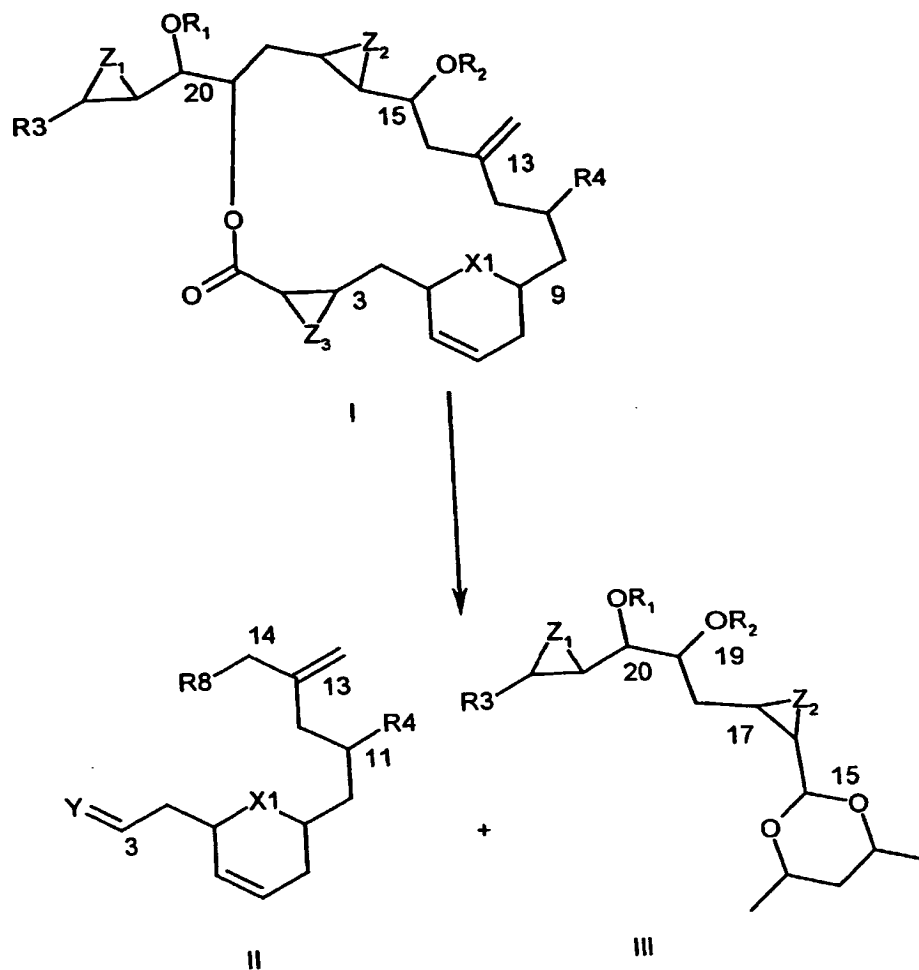
instant invention:

[0014] Further claimed matter are medicaments comprising one or more compounds of general formula I, optionally together with suitable formulations and vehicles, as described above.

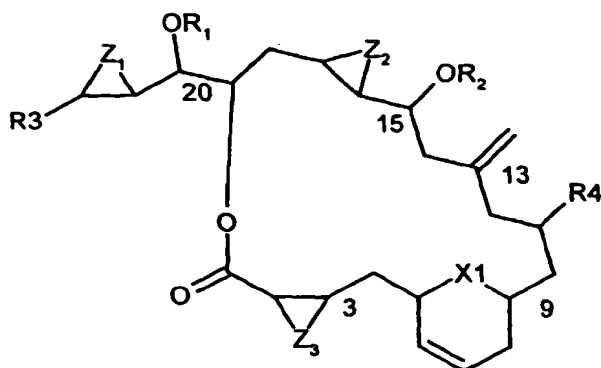
[0015] It has further been found that the inventive process for the production of laulimalide and laulimalide derivatives overcomes the known disadvantages of the state of the art process.

The retrosynthetic strategy of the process is illustrated in Scheme 1. The key step of the process is the Lewis acid mediated addition of compound II to the acetal moiety of compound III to form the C14 -15-bond.

Scheme 1

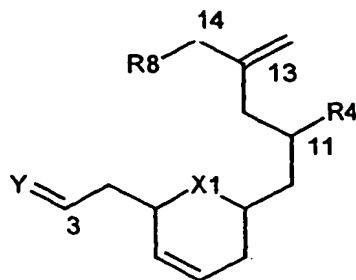


[0016] The instant invention therefore concerns a process for the production of laulimalide and laulimalide derivatives of general formula I



(I),

in which R^1 , R^2 , R^3 , R^4 , X_1 , Z_1 , Z_2 , Z_3 have the meaning as defined above, characterised in by reacting a compound of general formula II

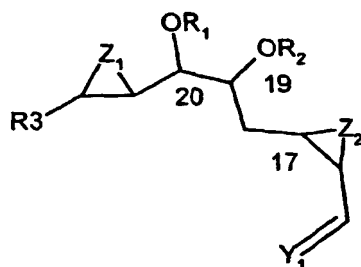


(II),

in which

- R^4 and X_1 have the meaning defined above under formula I, and
- R^8 has the meaning of hydrogen, trimethylsilyl, or the group $MHal$, wherein
- M has the meaning of Mg , Li , Ti , Ge or In , and
- Y has the meaning of oxygen or the group $=CH(OH)$, (Z) or $(E)-CH-COOH$, (Z) or $(E)-CH-COOR^9$ or (Z) or $(E)-CHHal$, in which
- R^9 has the meaning of hydrogen, alkyl, cycloalkyl or aryl,

with a compound of general formula III

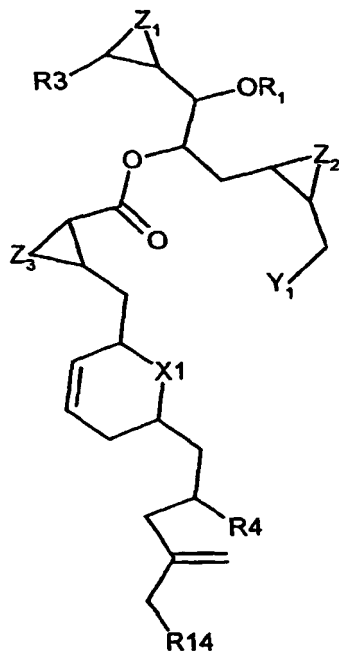


(III),

in which

R^1 , R^3 , Z_1 und Z_2 have the meaning defined above under formula I, and
 R^2 has the meaning of hydrogen, methylmethylether, paramethoxybenzyl, benzyl, or a protecting group, or a group $-COCH_2B$, wherein
 B has the meaning of the group $-SiR^{10}$, $-SeR^{11}$, $-Se(O)R^{11}$, $-TeR^{11}$, $-PO(OR^{11})_3$ or $-P(O)(OCH_2CR^{10})_2$, in which
 R^{10} has the meaning of alkyl, aryl, alkenyl, or the group $-CF_3$, or $-CH_2OR^{11}$, in which
 R^{11} has the meaning of hydrogen, alkyl, cycloalkyl or aryl, and
 Y_1 has the meaning of oxygen, or an alkyl acetal of the group $-CH(OR^{12})_2$, or a five membered O, O; N,O; O,S; or S,S; cyclic acetal, or six membered O,O; N,O; O,S; or S,S; cyclic acetal, and
 R^{12} has the meaning of alkyl,

to form an intermediate of general formula IV



(IV),

in which

R^1, R^3, R^4, X_1 and Z_1-Z_3 have the meaning defined above under formula I, and
 Y_1 has the meaning defined above under formula III, and
 5 R^{14} has the meaning of hydrogen, halogen, trimethylsilyl, or the group MHal, wherein
 M has the meaning of Mg, Li, Ti, Ge or In,

which is cyclized to the compounds of general formula I.

[0017] Preferred Laulimalid derivatives of general formula I are those, in which

10 R^1 and R^2 independently from each other have the meaning of hydrogen, α - C_1 - C_6 -alkyl, β - C_1 - C_6 -alkyl, methyl-methylether, C_1 - C_6 -alkyl optionally substituted with hydroxy, paramethoxybenzyl, benzyl, or a silyl protecting group, or an acetyl, benzyl, carbamate or carbonate protecting group,

15 R^3 has the meaning of a five or six membered, optionally substituted aryl or heteroaryl ring, or a five or six membered optionally substituted and optionally partially saturated C_3 - C_7 -cycloalkyl ring, which can be interrupted by oxygen, sulphur or the group $=NR^5$,

20 R^4 has the meaning of α - C_1 - C_6 -alkyl, β - C_1 - C_6 -alkyl, aryl or trifluoromethyl,

X_1 has the meaning of oxygen, sulphur or the group $=NR^5$, in which

R^5 has the meaning of hydrogen, C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl or aryl,

25 Z_1 has the meaning of a (Z)- or (E)-double bond, triple bond, or has the meaning of oxygen, sulphur or the group $-CH_2-$, $-CH_2-CH_2-$, $=C(OH)_2$, $=C(halogen)(OH)$, $=C(OH)NR^6$ or $=NR^7$,

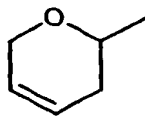
Z_2 has the meaning of a (Z)- or (E)-double bond, triple bond, or has the meaning of oxygen (α - or β -epoxide), sulphur or the group $-CH_2-$, $-CH_2-CH_2-$, $=C(OH)_2$, $=C(halogene)(OH)$, $=C(OH)NR^6$ or $=NR^7$,

30 Z_3 has the meaning of a (Z) or (E)-double bond,

R^6 has the meaning of C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl or aryl, and

35 R^7 has the meaning of hydrogen, C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl or aryl,

and the optical isomers and salts thereof, except of those compounds in which R^3 stands for the cycloalkyl ring



45 and X_1 has the meaning of oxygen, R^1 has the meaning of α -methyl, Z_1 has the meaning of a (E)-double bond, Z_2 has the meaning of β -epoxide if Z_3 has the meaning of a (Z)-double bond.

[0018] Especially preferred are those laulimalid derivatives of general formula I, according to claims 1 and 2, in which

50 R^1 and R^2 independently from each other have the meaning of hydrogen, α - C_1 - C_6 -alkyl, β - C_1 - C_6 -alkyl, methyl-methylether, C_1 - C_6 -alkyl optionally substituted with hydroxy, paramethoxybenzyl, benzyl, or a silyl protecting group, or an acetyl, benzyl, carbamate or carbonate protecting group,

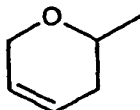
R^3 has the meaning of optionally substituted phenyl, biphenyl, naphthyl, thiophene, furan, oxazole, thiazole, imidazole, pyrazole, pyridin, pyrimidine, triazine, quinolin, isoquinolin or benzo derivatives thereof, or a
 55 a five or six membered optionally substituted and optionally partially saturated C_3 - C_7 -cycloalkyl ring, which can be interrupted by oxygen, sulphur or the group $=NR^5$,

R^4 has the meaning of α - C_1 - C_6 -alkyl, β - C_1 - C_6 -alkyl, phenyl, biphenyl, naphthyl, or trifluoromethyl,

X_1 has the meaning of oxygen, sulphur or the group $=NR^5$, in which

- R^5 has the meaning of hydrogen, C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, phenyl, biphenyl or naphthyl,
 Z_1 has the meaning of a (Z)- or (E)-double bond, triple bond, or has the meaning of oxygen, sulphur or the
 group $-CH_2-$, $-CH_2-CH_2-$, $=C(OH)_2$, $=C(halogen)(OH)$, $=C(OH)NR^6$ or $=NR^7$,
 Z_2 has the meaning of a (Z)- or (E)-double bond, triple bond, or has the meaning of oxygen (α - or β -epoxide),
 sulphur or the group $-CH_2-$, $-CH_2-CH_2-$, $=C(OH)_2$, $=C(halogen)(OH)$, $=C(OH)NR^6$ or $=NR^7$
 Z_3 has the meaning of a (Z) or (E)-double bond
 R^6 has the meaning of C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, phenyl, biphenyl or naphthyl, and
 R^7 has the meaning of hydrogen, C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, phenyl, biphenyl or naphthyl,

and the optical isomers and salts thereof, except of those compounds in which R^3 stands for the cycloalkyl ring



X_1 has the meaning of oxygen, R^1 has the meaning of α -methyl, Z_1 has the meaning of a (E)-double bond, Z_2 has the meaning of β -epoxide if Z_3 has the meaning of a (Z)-double bond.

[0019] Of special interest are those laulimalid derivatives of general formula I, in which

R^1 and R^2 independently from each other have the meaning of hydrogen, α - C_1 - C_6 -alkyl, β - C_1 - C_6 -alkyl, methyl-methylether, C_1 - C_6 -alkyl optionally substituted with hydroxy, paramethoxybenzyl, benzyl, or a silyl protecting group, or an acetyl, benzyl, carbamate or carbonate protecting group,

R^3 has the meaning of optionally substituted phenyl, biphenyl, naphthyl, thiophene, furan, oxazole, thiazole, imidazole, pyrazole, pyridin, pyrimidine, triazine, quinolin, isoquinolin or benzo derivatives thereof, or a five or six membered optionally substituted and optionally partially saturated C_3 - C_7 -cycloalkyl ring, which can be interrupted by oxygen, sulphur or the group $=NR^5$,

R^4 has the meaning of α - C_1 - C_6 -alkyl, β - C_1 - C_6 -alkyl, phenyl, biphenyl, naphthyl, or trifluoromethyl,

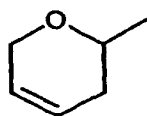
X_1 has the meaning of oxygen,

Z_1 has the meaning of a (Z)- or (E)-double bond, or has the meaning of oxygen,

Z_2 has the meaning of a (Z)- or (E)-double bond, or has the meaning of oxygen (α - or β -epoxide) and

Z_3 has the meaning of a (Z) or (E)-double bond,

and the optical isomers and salts thereof, except of those compounds in which R^3 stands for the cycloalkyl ring



X_1 has the meaning of oxygen, R^1 has the meaning of α -methyl, Z_1 has the meaning of a (E)-double bond, Z_2 has the meaning of β -epoxide if Z_3 has the meaning of a (Z)-double bond.

[0020] Of further special interest are those laulimalid derivatives of general formula I, in which

R^1 and R^2 independently from each other have the meaning of hydrogen, α - C_1 - C_6 -alkyl, β - C_1 - C_6 -alkyl, methyl-methylether, C_1 - C_6 -alkyl optionally substituted with hydroxy, paramethoxybenzyl, benzyl, or a silyl protecting group, or an acetyl, benzyl, carbamate or carbonate protecting group,

R^3 has the meaning of optionally substituted phenyl, 1,3-thiazoles or 2- and 3-pyridyl, or a six membered optionally substituted and optionally partially saturated cyclohexyl ring, which can be interrupted by oxygen,

R^4 has the meaning of α - C_1 - C_6 -alkyl, β - C_1 - C_6 -alkyl, phenyl, biphenyl, naphthyl, or trifluoromethyl,

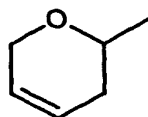
X_1 has the meaning of oxygen,

Z_1 has the meaning of a (Z)- or (E)-double bond, or has the meaning of oxygen,

Z_2 has the meaning of a (Z)- or (E)-double bond, or has the meaning of oxygen (α - or β -epoxide) and

Z_3 has the meaning of a (Z) or (E)-double bond,

and the optical isomers and salts thereof, except of those compounds in which R^3 stands for the cycloalkyl ring

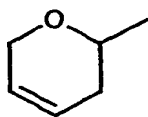


X_1 has the meaning of oxygen, R^1 has the meaning of α -methyl, Z_1 has the meaning of a (E)-double bond, Z_2 has the meaning of β -epoxide if Z_3 has the meaning of a (Z)-double bond.

[0021] Of most interest are those laulimalid derivatives of general formula I, in which

R^1 and R^2 independently from each other have the meaning of hydrogen, α - C_1 - C_6 -alkyl, β - C_1 - C_6 -alkyl, methyl-methylether, C_1 - C_6 -alkyl optionally substituted with hydroxy, paramethoxybenzyl, benzyl, or a silyl protecting group, or an acetyl, benzyl, carbamate or carbonate protecting group,

R^3 has the meaning of optionally substituted phenyl, 1,3-thiazoles, 2- or 3-pyridyl or the group



which is substituted with methyl,

R^4 has the meaning of α - C_1 - C_6 -alkyl, β - C_1 - C_6 -alkyl, phenyl, biphenyl, naphthyl, or trifluoromethyl,

X_1 has the meaning of oxygen,

Z_1 has the meaning of a (Z)- or (E)-double bond,

Z_2 has the meaning of a (Z)- or (E)-double bond, and

Z_3 has the meaning of a (Z) or (E)-double bond,

and the optical isomers and salts thereof.

[0022] Preferred protecting groups are silyl protecting groups, such as trimethylsilyl, triethylsilyl, tributylsilyl, tributyl-dipropyl-silyl, triisopropylsilyl, t-butyldiphenylsilyl or t-butyldimethylsilyl, or other protecting groups, such as for example acetyl, benzyl, carbamate or carbonate.

[0023] Halogene (Hal) has the meaning of chloro, bromo or iodine.

[0024] Alkyl stands for a substituted or unsubstituted, linear or branched alkyl chain, such as methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec. butyl, pentyl, iso-pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl.

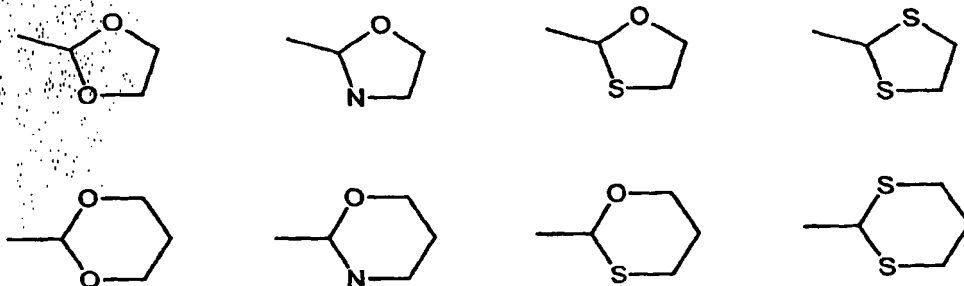
[0025] Cycloalkyl stands for a monocyclic alkyl ring, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl; and for a bicyclic ring or tricyclic ring, such as adamantanyl, which each can partially be saturated.

[0026] Alkenyl stands for a substituted or unsubstituted, linear or branched alkenyl chain, having 2 - 6, preferred 2 - 4 carbon atoms, such as vinyl, propen-1-yl, propen-2-yl, but-1-en-1-yl, but-1-en-2-yl, but-2-en-1-yl, but-2-en-2-yl, 2-methyl-prop-2-en-1-yl, 2-methyl-prop-1-en-1-yl, but-1-en-3-yl, but-3-en-1-yl, allyl.

[0027] Aryl has the meaning of a ring, consisting of 5 - 12 carbon atoms, such as naphthyl, biphenyl, and preferred a phenyl ring.

[0028] Heteroaryl has the meaning of a ring, consisting of 4 - 12 carbon atoms, which can be condensed with benzene. For example, a five membered ring has the meaning of thiophene, furan, oxazole, thiazole, imidazole, pyrazole or benzo derivatives thereof; and a six membered ring has the meaning of pyridin, pyrimidine, triazine, quinolin, isoquinolin or benzo derivatives thereof, and preferred thiazole and pyridin, especially 1,3-thiazole and 2- and 3-pyridyl.

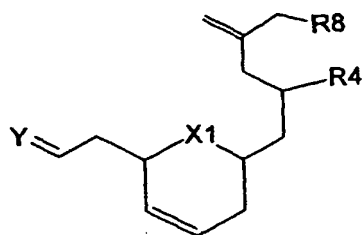
[0029] Cyclic acetal stands for a ring, such as



which can optionally be substituted with C₁-C₁₀-alkyl.

[0030] A further matter of the invention are the valuable intermediates which can preferably be used for the production of laulimalide and its derivatives.

Therefore, inventive matter are also the intermediates of general formula II

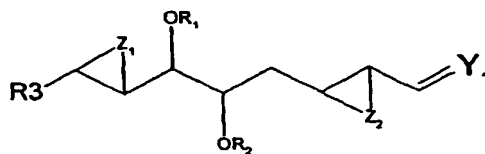


(II),

in which

- R⁴ and X₁ have the meaning defined above under formula I, and
 R⁸ has the meaning of hydrogen, trimethylsilyl, or the group MHal, wherein
 M has the meaning of Mg, Li, Ti, Ge or In, and
 Y has the meaning of oxygen or the group =CH(OH), (Z) or (E)-CH-COOH, (Z) or (E)-=CH-COOR⁹ or (Z) or (E)-CHHal, in which
 R⁹ has the meaning of hydrogen, alkyl, cycloalkyl or aryl,

the intermediates of general formula III



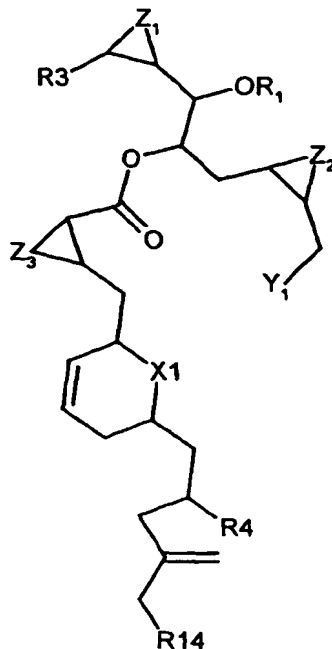
(III),

in which

R¹, R³, Z₁ and Z₂ have the meaning defined above under formula I, and

R^2 has the meaning of hydrogen, methylmethylether, paramethoxybenzyl, benzyl, or a protecting group, or a group $-\text{COCH}_2\text{B}$, wherein
 B has the meaning of the group $-\text{SiR}^{10}$, $-\text{SeR}^{11}$, $-\text{Se}(\text{O})\text{R}^{11}$, $-\text{TeR}^{11}$, $-\text{PO}(\text{OR}^{11})_3$ or $-\text{P}(\text{O})(\text{OCH}_2\text{CR}^{10})_2$, in which
 R^{10} has the meaning of alkyl, aryl, alkenyl, or the group $-\text{CF}_3$, or $-\text{CH}_2\text{OR}^{11}$, in which
 R^{11} has the meaning of hydrogen, alkyl, cycloalkyl or aryl, and
 Y_1 has the meaning of oxygen, or an alkyl acetal of the group $-\text{CH}(\text{OR}^{12})_2$, or a five membered O, O; N,O; O,S; or S,S; cyclic acetal, or six membered O,O; N,O; O,S; or S,S; cyclic acetal, and
 R^{12} has the meaning of alkyl,

and the intermediates of general formula IV



(IV),

in which

R^1 , R^3 , R^4 , X_1 and Z_1-Z_3 have the meaning defined above under formula I, and
 Y_1 has the meaning defined above under formula III, and
 R^{14} has the meaning of hydrogen, halogen, trimethylsilyl, or the group MHal , wherein
 M has the meaning of Mg, Li, Ti, Ge or In,

for the production of compounds of general formula I.

[0031] The intermediates of general formula II,



15

20

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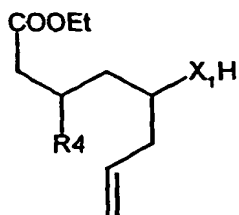
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5.



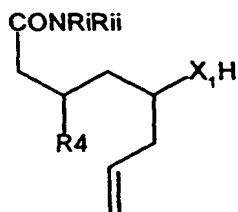
II-4),

in which R^4 and X_1 have the meaning as defined under formula I,

c) reacting compound II-4) with an amine of general formula II-4a



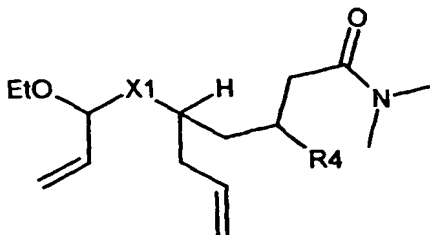
in which R^I and R^{II} independently from each other have the meaning of hydrogen or C_1 - C_6 -alkyl, to give a compound of general formula II-5)



II-5),

in which R^4 and X_1 have the meaning as defined under formula I and R^I and R^{II} have the meaning as defined under formula II-4a,

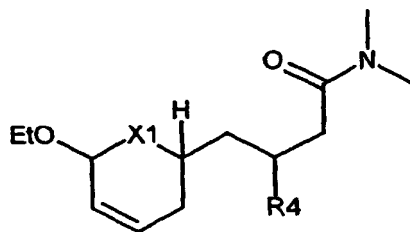
d) reacting compound II-5) in a suitable solvent with a suitable acetal and a suitable hydroxy compound to give a compound of general formula II-6)



II-6),

in which R^4 and X_1 have the meaning as defined under formula I,

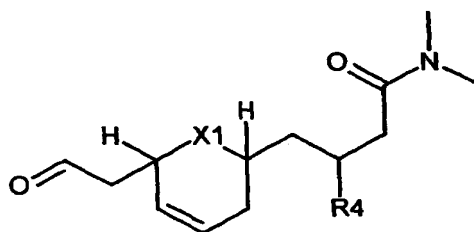
e) deoxygenating compound II-6) in a suitable solvent with a suitable catalyst, to give a compound of general formula II-7):



II-7),

in which R^4 and X_1 have the meaning as defined under formula I,

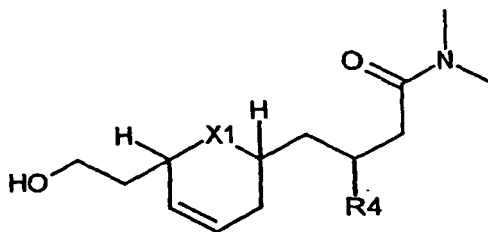
f) reacting compound II-7) with a suitable vinyl ether and a suitable perchlorate in a suitable solvent, to give a compound of general formula II-8)



II-8)

in which R^4 and X_1 have the meaning as defined under formula I,

g) reacting aldehyde compound II-8) with a suitable reductant in a suitable solvent to give an alcohol compound of general formula II-9)



II-9)

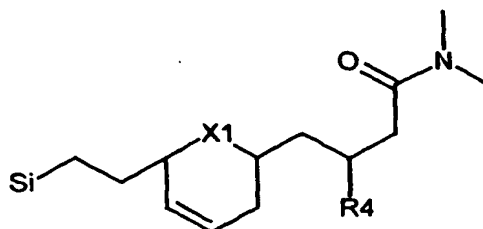
in which R^4 and X_1 have the meaning as defined under formula I,

h) reacting a solution of alcohol compound II-9) in a suitable organic base and with a silyl chloride or a triflalk (Si)

of general formula II-9a)



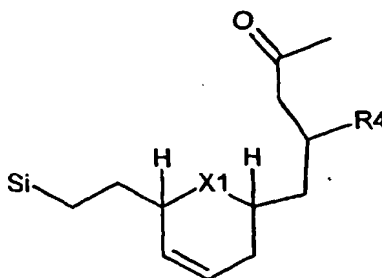
in which R^{21} , R^{22} and R^{23} independently from each other have the meaning of α - or β - C_1 - C_6 -alkyl, to give an amide compound of general formula II-10)



II-10)

in which R^4 and X_1 have the meaning as defined under formula I and Si has the meaning as defined under formula II-9a,

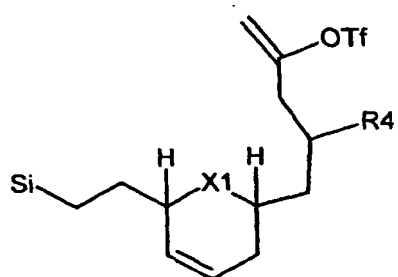
i) reacting amide compound of general formula II-10) with a metal organic compound and in a suitable solvent to give a ketone compound of general formula II-11).



II-11),

in which R^4 and X_1 have the meaning as defined under formula I and Si has the meaning as defined under formula II-9a,

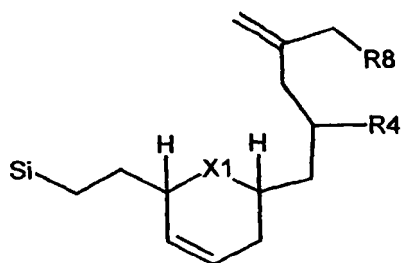
j) reacting the ketone compound II-11) with a suitable strong amide base in a suitable solvent, and accordingly with a suitable acylating agent in a suitable solvent to give an enoltriflate of general formula II-12)



II-12)

in which R^4 and X_1 have the meaning as defined under formula I and Si has the meaning as defined under formula II-9a,

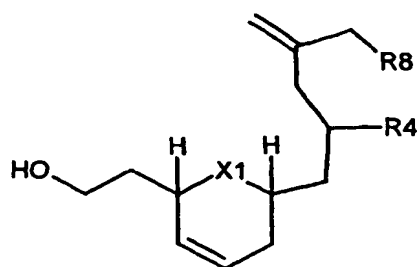
k) reacting enoltriflate compound II-12) with a suitable Pd catalyst and with alkali chloride in a suitable solvent, and accordingly with $TMSCH_2MgCl$ to give compound II-13)



II-13)

in which R^4 and X_1 have the meaning as defined under formula I, R^8 has the meaning as defined under formula II, and Si1 has the meaning as defined under formula II-9a,

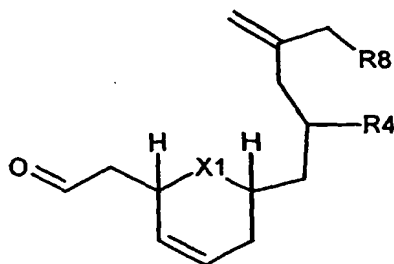
l) reacting compounds of general formula II-13) with a suitable ionic fluoride in a suitable solvent to give compound II-14)



II-14)

in which R^4 and X_1 have the meaning as defined under formula I, and R^8 has the meaning as defined under formula II,

m) reacting compound II-14) with a suitable oxidant in a suitable solvent to give an aldehyde compound of general formula II-15)



II-15)

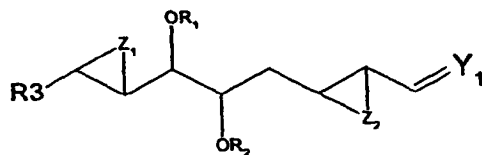
in which R^4 and X_1 have the meaning as defined under formula I, and R^8 has the meaning as defined under formula II, and

n) reacting aldehyde compound II-15) with a phosphonyl acetic ester of general formula II-15a)



in which R^x and R^y independently from each other have the meaning of C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl or phenyl, and with 18-crown-6, and a suitable strong amid base, in a suitable solvent to give the intermediate compound of general formula II).

The intermediates of general formula III,



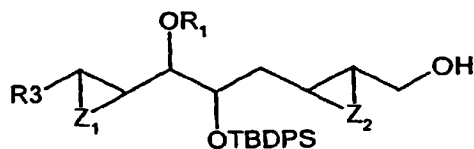
(III),

in which

R¹, R³, Z₁ and Z₂ have the meaning defined above under formula I, and
 R² has the meaning of hydrogen, methylmethylether, paramethoxybenzyl, benzyl, or a protecting group, or a group -COCH₂B, wherein
 B has the meaning of the group -SiR¹⁰, -SeR¹¹, -Se(O)R¹¹, -TeR¹¹, -PO(OR¹¹)₃ or -P(O)(OCH₂CR¹⁰)₂, in which
 R¹⁰ has the meaning of alkyl, aryl, alkenyl, or the group -CF₃, or -CH₂OR¹¹, in which
 R¹¹ has the meaning of hydrogen, alkyl, cycloalkyl or aryl, and
 Y₁ has the meaning of oxygen, or an alkyl acetal of the group -CH(OR¹²)₂, or a five membered O,O; N,O; O,S; or S,S; cyclic acetal, or six membered O,O; N,O; O,S; or S,S; cyclic acetal, and
 R¹² has the meaning of alkyl, can be produced via a process,

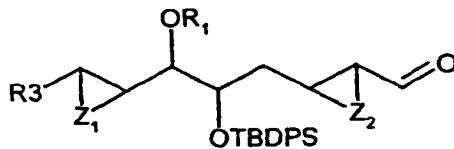
which is characterized in by reacting

o) an alcohol compound of general Formula III-16)



III-16),

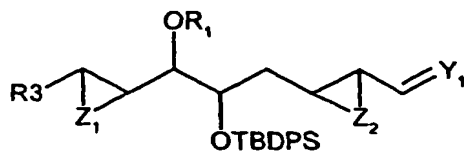
in which R¹, R³, Z₁ and Z₂ have the meaning as defined under general formula I, with a suitable oxidant in a suitable solvent to give an aldehyde compound of general formula III-17)



III-17),

in which R¹, R³, Z₁ and Z₂ have the meaning as defined under general formula I,

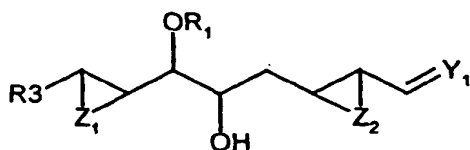
p) reacting a compound of general formula III-17) with an acetal in a suitable solvent to give a compound of general Formula III-18)



III-18),

in which R^1 , R^3 , Z_1 and Z_2 have the meaning as defined under general formula I, and Y_1 , has the meaning as defined under formula III,

q) reacting a compound of general formula III-18) with a suitable ionic fluoride in a suitable solvent to an alcohol compound of general formula III-19)



III-19),

in which R^1 , R^3 , Z_1 and Z_2 have the meaning as defined under general formula I, and Y_1 has the meaning as defined under formula III, and

r) reacting a compound of general formula III-19) with a suitable tertiary amine in a suitable solvent, and accordingly with a solution of a phosphoro acetyl chloride of general formula III-19a



in which R^9 has the meaning of C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl or aryl, in a suitable organic base to give a compound of general formula III.

[0032] According to the process for the production of the intermediates supra,

a suitable solvent in reaction step a), b), d), e), f), g), i), j), k), l), m), n), o), p), q) and r) is for example ether, tetrahydrofuran, methylene chloride, etc.;

a suitable oxidant in reaction step a), m) and o) is for example 1,1,1-triacetoxy-1,1-dihydro-1,2-benz-iodoxol-3(1H)-one (Dess-Martin periodinane), a combination of dimethylsulfoxide, oxalyl chloride or a tertiary amine (Swern-oxidation), etc.;

a suitable alkylating agent in reaction step b) is for example allyl-diisopinocampheyl-borane (lpc_2Ball), or alkyl-cyclopentadienyl-[2,2-dimethyl- α,α,α' -tetra-phenyl-1,3-dioxolanyl]-titanium, etc.;

a suitable acetal in reaction step d) and p) is for example acrolein-diethylacetal, etc.;

a suitable hydroxy compound in reaction step d) is for example an alcohol, such as ethanol, etc.;

a suitable vinyl ether in reaction step f) is for example vinyl-tert-butyl-dimethyl-silyl-ether, etc.;

a suitable catalyst in reaction step e) and f) is for example di-chloro-ditriphenyl-phosphino-benzylidene-ruthenium, etc.;

a suitable reductant in reaction step g) is for example sodium borohydride, lithium aluminium hydride, diisobutylaluminium-hydride, lithium borohydride, etc.;

a suitable metal organic compound in reaction step i) is for example methyl lithium, methyl magnesium bromide, etc.;

a suitable alkali chloride in reaction step k) is for example LiCl, NaCl, KCl, RbCl, CsCl, etc.,

a suitable a strong amide base in reaction step j) and n) is for example KHMDS, NaHMDS, LDA, dicyclohexyl-isopropyl-

lithium amide, etc.;

a suitable acylating agent in reaction step j) is for example $\text{PhN}(\text{OTf})_2$ or Ti_2O , tosyl chloride, mesyl chloride, etc.;

a suitable Pd catalyst in reaction step k) is for example $\text{Pd}(\text{Ph}_3\text{P})_4$, tris-di-benzylideneacetone-dipalladium, etc.;

a suitable ionic fluoride in reaction step l) and q) is for example tetra-n-butylammoniumfluoride (TBAF), hydrogen fluoride in acetonitrile, pyridine, etc.;

a suitable tertiary amine in reaction step r) is for example 4-dimethylamino-pyridine (DMAP), pyridine, collidine, etc.;

a suitable organic base in reaction step h) and r) is for example triethylamine, pyridine, 2,6-ditert-butylpyridine, ethyl-diisopropyl amine, etc.;

a suitable perchlorate in reaction step f) is for example lithium perchlorate, etc.

[0033] The following process examples describe the production of the inventive intermediate compounds, and further describe the feasibility of the inventive process, however, not restricting the process to compounds described in these process examples.

1.0 Process Examples

1.1 In General

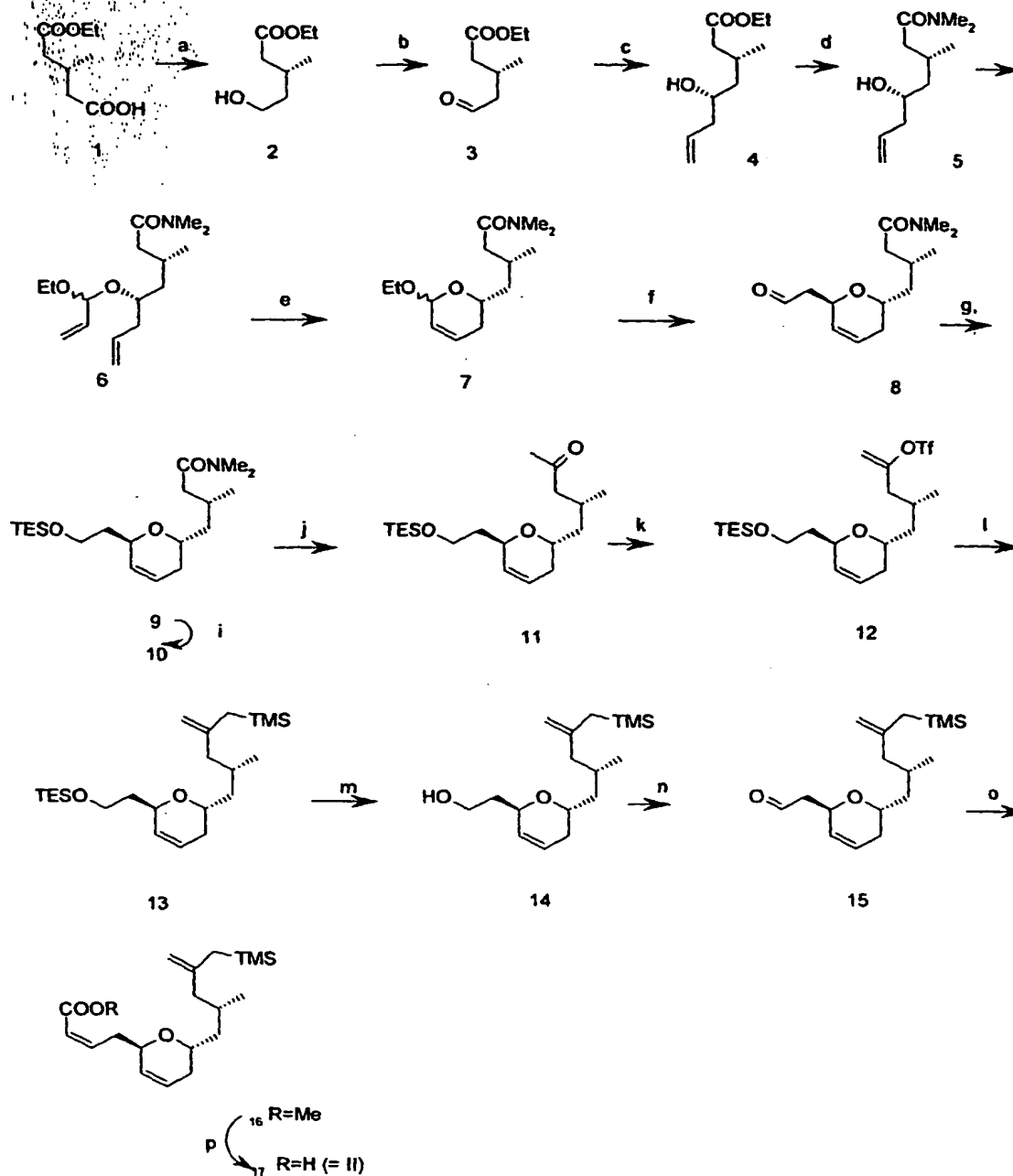
[0034] Unless otherwise stated, solvents were dried by distillation under argon, from Na (toluene), Na / K (Et_2O), potassium (THF), CaH_2 (Et_3N , DMF), P_2O_5 (CH_2Cl_2), KOH (pyridine) and Mg (MeOH, EtOH). All other commercially available reagents were used without further purification unless specified otherwise. All reactions were performed in oven-dried glassware under argon. Chromatography refers to flash column chromatography on silica gel 60 (230-400 mesh). Thin layer chromatography (TLC) was performed on Al-backed plates (Merck silica gel 60 F_{254}) and visualised by using either a UV lamp, phosphomolybdic acid, sulphuric acid/anisaldehyde or potassium permanganate solutions. Melting points (mp) are uncorrected. Optical rotations are reported in g/100 ml. Infrared spectra (IR) were measured as evaporated films on single crystal silica plates and reported in wave numbers (cm^{-1}) with broad signals denoted by (br). High resolution mass spectra were obtained using electron ionisation (EI), field ionisation (FI) or fast atom bombardment (FAB). ^1H and ^{13}C NMR were recorded on a Bruker AC 250 (250 MHz), AM 400 (400 MHz) or AM 600 (600 MHz) spectrometer. Chemical shifts are reported using the solvent resonance internal standard (chloroform, 7.26 and 77.0 ppm).

1.2 Process for the production of the used intermediates

1.2.1 Process for the production of intermediate compound II

[0035] The production of compound II, in which R^4 has the meaning of β -methyl, R^8 has the meaning of trimethylsilyl, X_1 has the meaning of oxygene, and Y has the meaning of group (Z)- $=\text{COOMe}$, was performed according to Scheme 2.

Scheme 2



Reagents and conditions

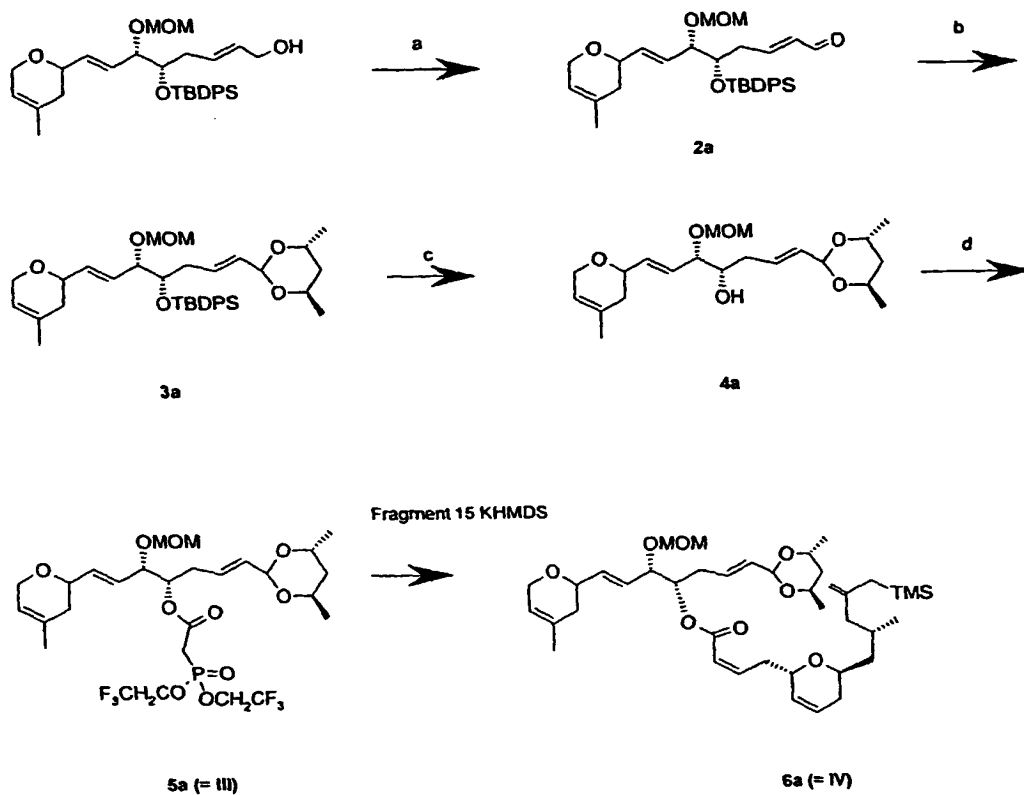
[0036]

a) $\text{BH}_3 \cdot \text{Me}_2\text{S}$, 98%; b) Et_2NH , EtOH , 94%; c) Swern ox., 96%; d) AllylTi TADDOL , 92%; e) acrolein -diethylacetal, TsOH , Tol , 94%; f) 4 mol % Grubs catalyst, CH_2Cl_2 , 87%; g) NaBH_4 , MeOH , 0°C , 99%; i) TESCl , Py , Tol , 92%; j) MeLi , Et_2O , $-75^\circ\text{C} \rightarrow \text{r.t.}$, 90%; k) KHMDS , $\text{C}_6\text{H}_5\text{N}(\text{OTf})_2$, THF , 60%; l) 5 mol% $\text{Pd}(\text{PPh}_3)_4$, LiCl 5 eqv, $\text{TMSCH}_2\text{MgBr}$ 5 eqv, Et_2O , 96%; m) K_2CO_3 , MeOH , 0°C , 98%; n) $\text{Py} \cdot \text{SO}_3$, TEA , DMSO , CH_2Cl_2 , 90%; o) $\text{MeOOCCH}_2\text{P}(\text{O})-(\text{OCH}_2\text{CF}_3)_2$, KHMDS , THF , 84%; p) $\text{LiCl} \cdot \text{H}_2\text{O}$, acetone , 0°C , 2 days, 80%.

1.2.2 Process for the production of intermediate compounds III and IV

[0037] The synthesis of intermediate compound III (R^1 = methylmethylether (MOM), R^2 = group $-\text{COCH}_2\text{B}$, $\text{B} = -\text{P}(\text{O})(\text{OCH}_2\text{CR}^{10})_2$, $\text{R}^{10} = -\text{CF}_3$ (TBDPS), R^3 = methyl, X = oxygene, Y = chiral six membered cyclic acetal, Z and Z_1 = double bond) and intermediate compound IV (R^1 = methylmethylether (MOM), R^3 = methyl, X , X_1 = oxygene, Z and Z_1 = (E)-double bonds, R^2 = trimethylsilyl (TMS), Z_3 = (Z)-double bond, R^4 = α -methyl) was performed according to Schemes 3 and 4.

Scheme 3

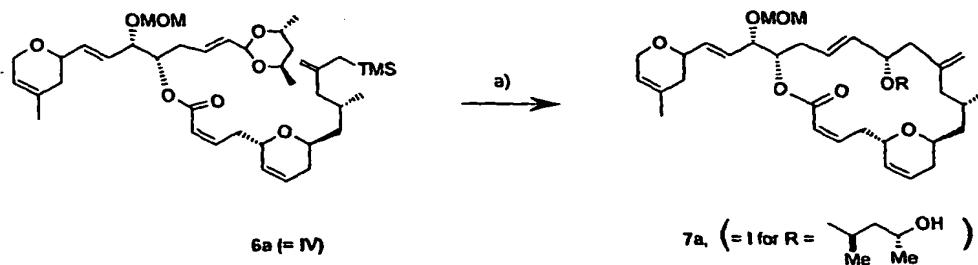


[0038] Reagents and conditions: a) Dess-Martin oxidation 96%, b) (R;R)-(-)-2,4 pentan diol/ H^+ , 89%, c) TBAF, THF 96%, d) $(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(\text{O})\text{CH}_2\text{COCl}/\text{DMAP}/\text{Py}$, -78°C -r.t., 96%,

1.2.3 Process for the production of inventive compounds from intermediate of formula IV

[0039]

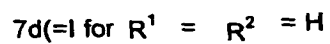
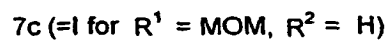
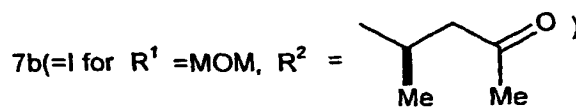
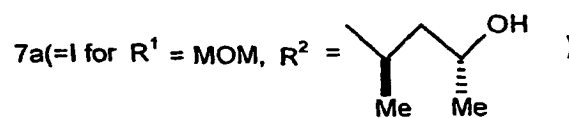
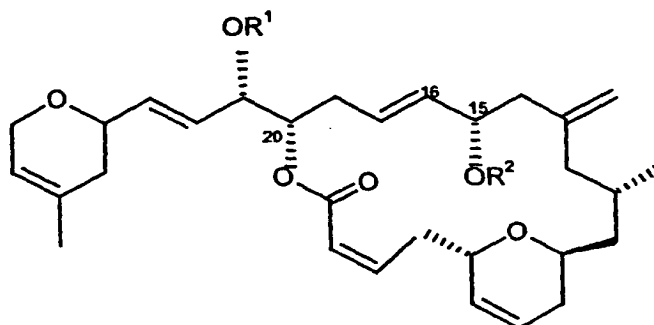
Scheme 4

[0040] Reagents and conditions: a) EtAlCl_2 , methylene chloride, $-50-0^\circ\text{C}$, 85%.

1.2.4 Process for the selective removal of the O-15- and O-20-protecting groups and for the selective epoxidation of the 16,17-double bond, selective derivatization of intermediates of formula I (Scheme 5)

[0041]

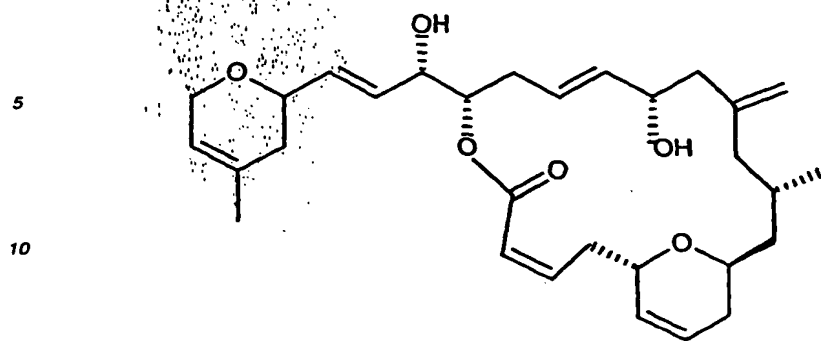
Scheme 5



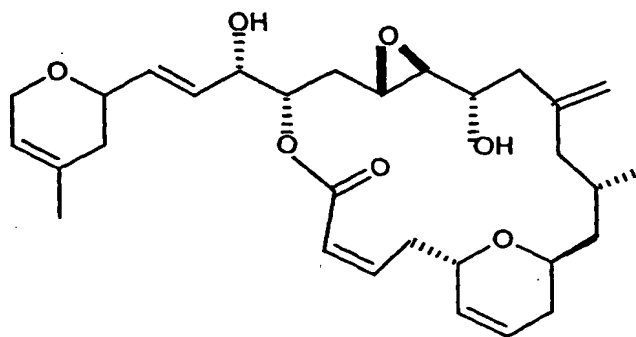
a

b

c



d



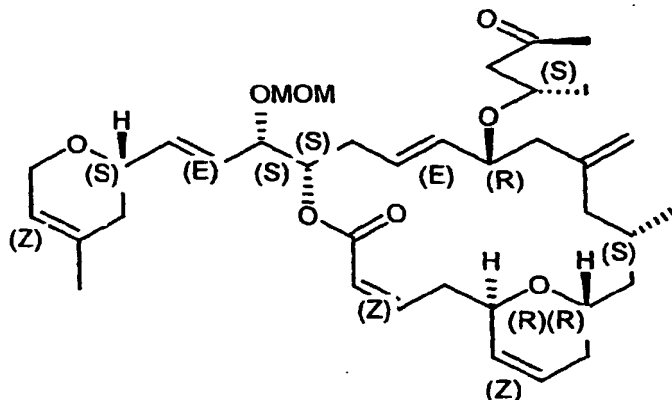
7e (=), laulimalide)

Reagents and Conditions:

[0042]

- 45 a) Dess Martin periodinane, ether, 90%; b) pTsOH, CH₂Cl₂, 80%;
c) Me₂BBr, ether, -78°C, 96%; d) tBuOOH, Ti(OiPr)₄, CH₂Cl₂, -20°C, 2h
- 50
- 55

Compound 7b.



$C_{37}H_{54}O_8$

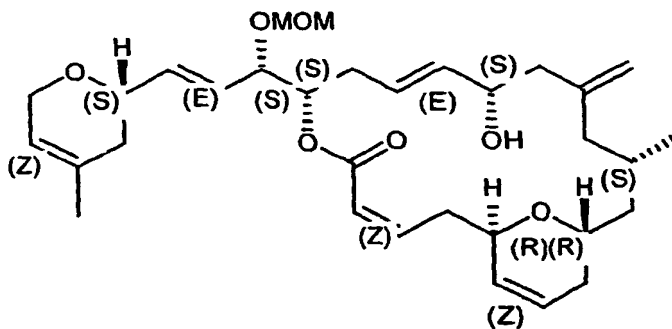
Exact Mass: 626.3819

Mol.Wt: 626.8199

C, 70.90; H, 8.68; O, 20.42

[0043] A solution of alcohol **7a** (0.02g, 0.032mmol) in dry CH_2Cl_2 (0.5ml) was added to a slurry of Dess-Martin periodinane (0.02g, 0.06mmol) and $NaHCO_3$ (0.05g) in CH_2Cl_2 (2 ml). The mixture was stirred at room temperature for 30 minutes, then subjected directly to SiO_2 Flash chromatography (hexane : ethyl acetate - 1:1) to yield **7b** as a colorless oil (0.018g, 90%), $[\alpha]_D^{20} = -35^\circ$ ($c=0.05$ in $CHCl_3$); IR (neat): 2978, 1719, 1682, 1640, 1360, 1166, $1035cm^{-1}$; 1H -NMR (600 MHz, $CDCl_3$); δ in ppm= 6.34 (ddd, $J=11.5, 10.0, 5.5$ Hz), 5.93 (1H, d, $J=11.6$ Hz), 5.85 (2H, m), 5.71 (1H, ddd, $J=10.2, 4.2, 2.4$ Hz), 5.62 (1H, m), 5.58 (2H, m), 5.44 (2H, m), 5.09 (1H, dd, $J=12.9, 6.4$ Hz), 4.80 (1H, brs), 4.77 (1H, brs), 4.69 (1H, d, $J=6.8$ Hz), 4.57 (1H, d, $J=6.8$ Hz), 4.27 (1H, m), 4.16 (2H, m), 4.16 (2H, m), 4.07 (1H, m), 3.94 (2H, m), 3.83 (1H, ddd, $J=8.3, 8.0, 4.7$ Hz), 3.69 (1H, m), 3.40 (3H, s), 2.69 (1H, dd, $J=15.3, 6.9$ Hz), 2.42 (1H, dd, $J=15.3, 6.0$ Hz), 2.37 (2H, m), 2.26 (1H, dd, $J=14.6, 7.9$ Hz), 2.16 (3H, s), 2.12 (1H, m), 2.06 (3H, m), 1.90 (2H, m), 1.74 (2H, m), 1.65 (3H, brs), 1.62 (3H, m), 1.16 (1H, m), 1.14 (3H, d, $J=6.3$ Hz), 0.91 (1H, m), 0.87 (3H, d, $J=6.2$ Hz); ^{13}C -NMR (150 MHz, $CDCl_3$), δ in ppm=208.2 (s), 165.7 (s), 147.7 (d), 144.9 (s), 136.2 (d), 134.7 (d), 131.7 (s), 128.9 (d), 127.9 (d), 126.3 (d), 125.4 (d), 121.8 (d), 120.1 (d), 113.6 (t), 94.4 (t), 77.4 (d), 76.1 (d), 74.3 (d), 73.6 (d), 72.4 (d), 69.0 (d), 67.4 (d), 65.9 (t), 56.0 (d), 51.7 (q), 45.3 (t), 43.2 (t), 42.9 (t), 36.0 (t), 34.5 (t), 33.3 (t), 31.8 (t), 31.7 (d), 28.9 (q), 23.3 (q), 20.6 (q), 19.8 (q); HRMS: found: 626. 8100, $C_{37}H_{54}O_8$ requires 626.8199.

Compound 7c



$C_{32}H_{46}O_7$

Exact Mass: 542.3244

10

15

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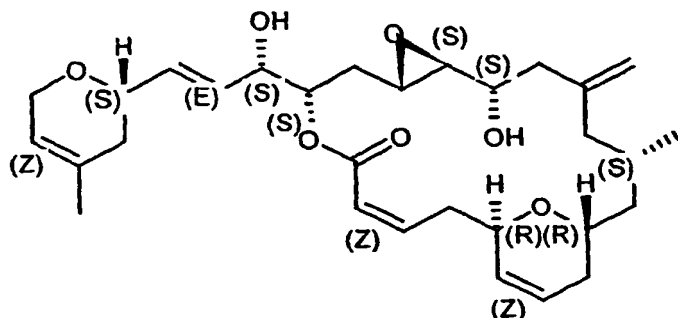


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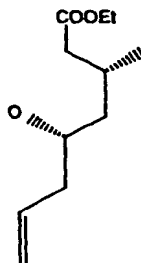
50

CCOC(=O)[C@H](C)CC=O

1717, 1415, 1360, 1238, 1182, 940 cm^{-1} ; $^1\text{H-NMR}$ (250 MHz, CDCl_3); δ in ppm = 9.80 (1H, s), 4.25 (2H, q, $J=7.5$ Hz), 3.75 (3H, m), 2.8-2.2 (5H, m), 1.22 (3H, t, $J=7.5$ Hz), 1.05 (3H, d, $J=7.2$ Hz); $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3); δ in ppm = 204.0 (d), 168.2 (s), 60.8 (t), 50.4 (t), 41.4 (t), 25.7 (d), 20.4 (q), 14.6 (q); HRMS: found 158,0450 \pm 5 ppm, $\text{C}_8\text{H}_{14}\text{O}_3$ requires 158,0943

ii) Process for the production of compound 4

[0050]



$\text{C}_{11}\text{H}_{20}\text{O}_3$

Exact Mass: 200,1412

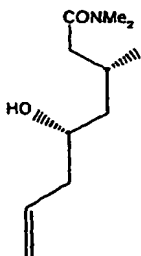
Mol. Wt.: 200,2747

C, 65,97; H, 10,07; O, 23,97

[0051] Aldehyde compound 3 of step i) (0.6 g, 3.8 mmol) was dissolved in dry Et_2O (20 ml) and cooled to -100°C . To this solution was added (-) Ipc_2BAI (9 ml, 0.5 M in pentane, 1.2 eqv) by cannulation during 30 min. After the completion of the addition, the mixture was stirred at the same temperature for 30 min. Methanol (1 ml) was added at -100°C and the reaction mixture was allowed to reach room temperature. The solvent was evaporated and the residue was dissolved in THF (20 ml). To this solution was added a solution of sodium perborate (1g in 10 ml water,) and the mixture was stirred for 30 min. The organic phase was separated and the water phase was extracted with ethyl acetate (3 X 5 ml). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. Flash chromatography of the crude mixture (ethyl acetate : hexane -5:1) provided 4. (0.66 g, 87%), oil, $[\alpha]_D^{20} = -9.4^\circ$ ($c = 0.65$, CHCl_3); IR (neat) 3460, 2925, 1730, 1633, 1499, 1460, 1397, 1262, 809 cm^{-1} ; $^1\text{H-NMR}$ (250 MHz, CDCl_3); δ in ppm = 5.86 (1H, m), 5.11 (2H, brd, $J=14.0$ Hz), 4.16 (2H, q, $J=7.0$ Hz), 3.75 (1H, brd, $w_{1/2} = 17\text{Hz}$), 2.4-1.9 (5H, m), 1.45 (1H, m), 1.32 (1H, m), 1.24 (3H, t, $J=7.0$ Hz), 0.99 (3H, d, $J=6.5$ Hz); $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3); δ in ppm = 173.5 (s), 132.9 (d), 118.9 (t), 71.6 (d), 60.6 (t), 44.0 (t), 43.2 (t), 42.6 (t), 27.6 (d), 19.9.4 (q), 14.6 (q); 27.6 (d), 19.9.4 (q), 14.6 (q); MS-EI (m/z , %): 200 (M^+ , 0.3), 182 ($\text{M}^+ - \text{H}_2\text{O}$, 20), 172 (25), 158 (20), 128 (12), 85 (83), 72 (100); HRMS: found 1821, 1310 \pm 5 ppm, $\text{C}_{11}\text{H}_{18}\text{O}_2$ ($\text{M}^+ - \text{H}_2\text{O}$) requires 182,1307.

iii) Process for the production of compound 5

[0052]



$\text{C}_{11}\text{H}_{21}\text{NO}_2$

Exact Mass: 199,1572

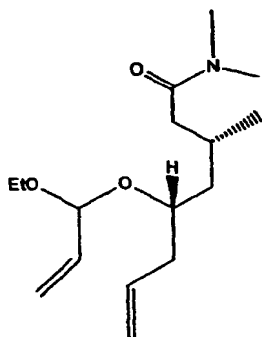
Mol. Wt.: 199,2900

C, 66,29; H, 10,62; N, 7,03; O, 1606

[0053] A solution of alcohol compound 4 of step ii) (0.6 g, 3mmol) in dimethylamine (5.6 M in ethanol, 10 ml) was heated for 2h in sealed flask at 40°C and then, was allowed to stay 12 h at room temperature. The ethanol was removed and the residue was filtered through SiO_2 , (CH_2Cl_2 : MeOH - 97:3) to give pure amide 5 (0.58 g, 98%) as a yellow oil; $[\alpha]_D^{20} = -9.4^\circ$ ($c = 0.65$ in CHCl_3); IR (neat) 3665, 3645, 3400, 2925, 1633, 1504, 1403, 1056, cm^{-1} ; $^1\text{H-NMR}$ (250 MHz, CDCl_3); δ in ppm = 5.86 (1H, m), 5.11 (2H, brd, $J = 14.0$ Hz), 3.01 (3H, s), 2.96 (3H, s), 3.75 (1H, brs, $w_{1/2} = 19\text{Hz}$), 2.4-2.2 (5H, m), 1.45 (2H, m), 0.99 (3H, d, $J = 6.5$, Hz); $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3), δ in ppm = 175.5 (s), 135.6 (d), 117.8 (t), 69.7 (d), 44.6 (t), 43.3 (t), 41.3 (t), 37.7 (q), 35.8 (q), 27.6 (d), 21.2 (q); MS-EI (m/z , %): 199 (M^+ , 0.5), 188 ($\text{M}^+ - \text{H}_2\text{O}$, 15), 172 (20), 158 (32), 128 (12), 95 (23), 85 (83), 72 (100); HRMS: found 181,1470 \pm 5 ppm, $\text{C}_{11}\text{H}_{19}\text{O}_2\text{N}$ ($\text{M}^+ - \text{H}_2\text{O}$) requires 181,1466.

iv) Process for the production of compound 6

[0054]



$\text{C}_{16}\text{H}_{29}\text{NO}_3$

Exact Mass: 283,2147

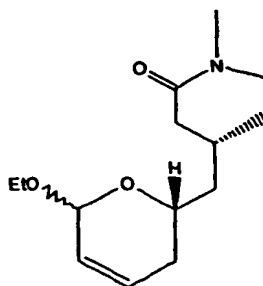
Mol. Wt.: 283,4064

C, 67,81; H, 10,31; N, 4,94; O, 16,94

[0055] To a solution of compound 5 of step iii) (0.350 g, 1.7 mmol) and acrolein-diethylacetal (0.38 ml, 2.4 mmol) in dry toluene (30 ml) was added TsOH (10 mg) and the mixture was slowly rotated on a rotavapour at 80°C mbars and 40°C. The reaction was monitored by TLC and the volume of the solvent was kept constant by addition of toluene. At the end of the reaction, the mixture was washed with NaHCO_3 , water, brine, dried (Na_2SO_4) and concentrated. Purification by Flash chromatography (ethyl acetate : toluene - 3:1) provided compound 6 (0.46 g, 92%), as a mixture of diastereomers (1:1); IR (neat) 3041, 3077, 2925, 1651, 1451, 1497, 1324, 1262, 1181, 1103 cm^{-1} ; $^1\text{H-NMR}$ (250 MHz, CDCl_3); δ in ppm = 5.81 (4H, m), 5.40 (2H, d, $J = 16.2$, Hz), 5.28 (2H, d, $J = 12.6$, Hz), 5.10 (4H, m), 4.97 (1H, d, $J = 5.3$, Hz), 4.91 (1H, d, $J = 5.5$, Hz), 3.50 (4H, m), 3.01 (6H, s), 2.94 (6H, s), 2.50-1.56 (12H, m), 1.37 (2H, m), 1.17 (6H, t, $J = 7.0$ Hz), 1.0 (3H, d, $J = 6.2$ Hz), 0.95 (3H, d, $J = 6.2$ Hz); $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3), δ in ppm = 172.7 (s), 172.6 (s), 136.4 (d), 136.3 (d), 135.3 (d), 134.9 (d), 118.3 (t), 118.2 (t), 117.6 (t), 117.5 (t), 102.4 (d), 100.0 (d), 75.00 (d), 75.55 (d), 60.8 (t), 60.7 (t), 42.5 (t), 42.2 (t), 41.6 (t), 41.5 (t), 40.4 (t), 39.5 (t), 37.9 (q), 37.7 (q), 35.7 (q), 27.2 (d), 20.6 (q), 20.3 (q), 15.6 (q), 15.5 (q); HRMS: found 283,2155 \pm 5 ppm, $\text{C}_{16}\text{H}_{29}\text{NO}_3$ requires 283,2147

v) Process for the production of compound 7

[0056]

 $C_{14}H_{25}NO_3$

Exact Mass: 255,1834

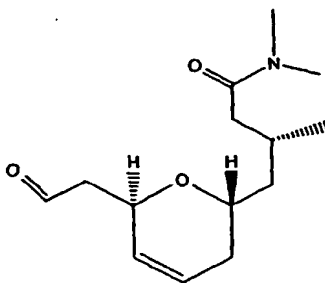
Mol. Wt.: 255,3532

C, 67,85; H, 9,87; N, 5,49; O, 18,80

[0057] A solution of compound 6 of step iv) (0.42 g, 1.5 mmol) and Grubs catalyst (0.06 g, 0.007 mmol) in CH_2Cl_2 was deoxygenated by a freeze-thaw cycle in which the solvent was first frozen in liquid N_2 , and then warmed up in vacuo. The deoxygenated mixture was refluxed for a 6 h (TLC monitoring). At the end of the reaction the catalyst was destroyed by passing an air through the solution for 15 min. The solvent was evaporated and the crude product was purified by Flash chromatography (ethyl acetate : toluene : TEA-3:1.0.1) to give 7 as a mixture of diastereomers (1:1) (0.35 g, 92%), oil; IR (neat) 3041, 2925, 1644, 1455, 1395, 1324, 1262, 1181, 1103 cm^{-1} ; 1H -NMR (250 MHz, $CDCl_3$); δ in ppm = 5.95 (2H, m), 5.75 (1H, d, $J=10.6$ Hz), 5.66 (1H, d, $J=10.6$ Hz), 5.04 (1H, brs), 4.96 (1H, brs), 3.90 (4H, m), 3.54 (2H, m), 3.01 (6H, s), 2.94 (6H, s), 2.50-1.80 (12H, m), 1.65 (2H, m), 1.2 (6H, t, $J=6.9$ Hz) 1.0 (3H, d, $J=6.2$ Hz), 0.95 (3H, d, $J=6.2$ Hz); ^{13}C -NMR (62.5 MHz, $CDCl_3$), δ in ppm = 172.7 (s), 172.6 (s), 129.4 (d), 128.1 (d), 126.0 (d), 98.1 (d), 94.8 (d), 70.69 (d), 64.4 (d), 64.0 (t), 63.5 (t), 43.1 (t), 43.0 (t), 41.4 (t), 37.9 (q), 35.7 (q), 31.7 (t), 31.5 (t), 27.5 (d), 26.9 (d), 20.5 (q), 19.8 (q), 15.7 (q); HRMS: found 255,1840 \pm 5 ppm, $C_{14}H_{25}NO_3$ requires 255,1834.

vi) Process for the production of compound 8

[0058]

 $C_{14}H_{23}NO_3$

Exact Mass: 253,1678

Mol. Wt.: 253,3374

C, 66,37; H, 9,15; N, 5,53; O, 18,95

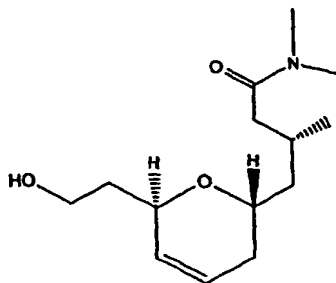
[0059] A mixture of compound 7 of step v) (0.12 g, 0.47 mmol), vinyl-TBS ether (0.1 g, 0.62 mmol) and a solution of $LiClO_4$ in ethyl acetate (5 ml, 3M) was kept at room temperature for 24 h. The mixture was diluted with water (10 ml) and the organic phase was separated. The water phase was extracted with $CHCl_3$ (3 X 5 ml). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. Purification by Flash chromatography (ethyl acetate : toluene -3:1) provided 8 (0.105 g, 89%), oil, $[\alpha]_D^{20} = -8.8^\circ$ ($c=0.5$ in $CHCl_3$); IR (neat) 2925, 1724, 1633, 1499,

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1460, 1461, 1397, 1262, 809 cm^{-1} ; $^1\text{H-NMR}$ (250 MHz, CDCl_3); δ in ppm = 9.79 (1H, dd, $J=3, 1.7$ Hz), 5.75 (1H, ddd, $J=10.3, 5, 2.5$ Hz), 5.68 (1H, ddd, $J=10.3, 4, 2.5$ Hz), 4.90 (1H, m), 3.78 (1H, m), 2.98 (3H, s), 2.82 (3H, s), 2.70 (1H, ddd, $J=16.0, 8.8, 3$ Hz), 2.52 (1H, ddd, $J=16, 4.7, 1.7$ Hz), 2.2-2.1 (4H, m), 1.9 (1H, m), 1.80 (1H, m), 1.10 (1H, m), 0.90 (3H, d, $J=6.2$ Hz); $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3); δ in ppm = 201.4 (d), 172.6 (s), 128.2 (d), 125.7 (d), 67.8 (d), 66.4 (d), 48.4 (t), 41.4 (t), 37.9 (q), 35.8 (q), 31.0 (t), 26.9 (d), 20.2 (q); MS-EI (m/z , %): 253 (M^+ , 8), 238 (3), 180 (15), 156 (9), 126 (12), 95 (15), 87 (100); HRMS: found 253,1662 \pm 5 ppm, $\text{C}_{14}\text{H}_{23}\text{NO}_3$ requires 253,1678.

vii) Process for the production of compound 9

[0060]



$\text{C}_{14}\text{H}_{25}\text{NO}_3$

Exact Mass: 255,1834

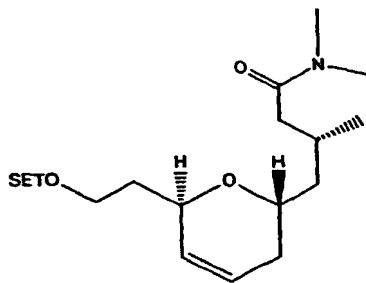
Mol. Wt.: 255,3532

C, 66,85; H, 9,87; N, 5,49; O, 18,80

[0061] Reduction of aldehyde compound 8 of step vi) (0.140 g, 0.55mmol) was performed in MeOH (3ml) with NaBH_4 (0.015g) at 0°C . The reaction was quenched with 0.5 ml saturated solution of NH_4Cl , the solvent was evaporated and the mixture was extracted with ethyl acetate (3 X 5 ml). The combined extracts were washed with water followed by brine, dried (Na_2SO_4) and concentrated to give pure alcohol of compound 9 (0.14 g) which was used in the next step without further purification. IR (neat) 3650, 3500, 3030, 2953, 2876, 1653, 1495, 1460, 1415, 1394, 1263, 1089 cm^{-1} ; $^1\text{H-NMR}$ (250 MHz, CDCl_3); δ in ppm = 5.75 (1H, brd, $J=10.3$ Hz), 5.65 (1H, brd, $J=10.3$ Hz), 4.36 (1H, brd, $J=9.8$ Hz), 3.70 (3H, m), 2.98 (3H, s), 2.82 (3H, s), 2.3-2.1 (4H, m), 1.9-1.5 (4H, m), 1.20 (1H, m), 0.94 (3H, d, $J=6.4$ Hz); $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3); δ in ppm = 172.6 (s), 129.9 (d), 124.3 (d), 70.1 (d), 66.4 (d), 60.4 (t), 42.1 (t), 41.4 (t), 37.8 (q), 36.7 (t), 35.8 (q), 31.0 (t), 27.0 (d), 20.3 (q); MS-EI (m/z , %): 255 (M^+ , 8), 237 (3), 210 (28), 182 (15), 158 (16), 140 (12), 128 (14), 114 (17), 95 (15), 87 (100), 72 (84); HRMS: found 255,1816 \pm 5 ppm, $\text{C}_{14}\text{H}_{25}\text{NO}_3$ requires 255,1834.

viii) Process for the production of compound 10

[0062]



$\text{C}_{20}\text{H}_{39}\text{NO}_3\text{Si}$

Exact Mass: 255,1834

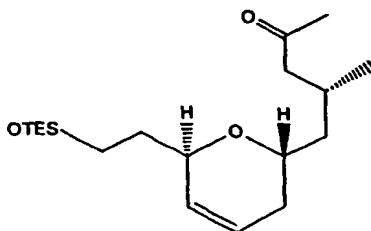
Mol. Wt.: 369,6141

C, 64,99; H, 10,64; N, 3,79; O, 12,99; Si, 7,60

[0063] To a solution of compound 9 of step vii) (0.13 g, 0.5 mmol) in pyridine (5 ml) was added TESCl (0.12 ml, 0.7 mmol) and the mixture was stirred at room temperature for 30 min. The mixture was diluted with toluene (10 ml), washed with water, brine, dried (Na_2SO_4) and concentrated. The crude product was purified by Flash chromatography (hexane : ethyl acetate - 1:1) to give compound 10 (0.18 g, 98 %), oil, $[\alpha]_D^{20} = -20.0^\circ$ ($c = 0.60$, CHCl_3); IR (neat) 3030, 2953, 2915, 2876, 1653, 1495, 1460, 1415, 1394, 1263, 1089 cm^{-1} ; $^1\text{H-NMR}$ (250 MHz, CDCl_3); δ in ppm = 5.76 (1H, brd, $J = 10.3$ Hz), 5.65 (1H, brd, $J = 10.3$ Hz), 4.28 (1H, m), 3.70 (3H, m), 2.98 (3H, s), 2.90 (3H, s), 2.3-2.1 (3H, m), 1.9-1.5 (5H, m), 1.20 (1H, m), 0.94 (3H, d, $J = 6.4$ Hz), 0.90 (9H, t, $J = 7.5$ Hz), 0.60 (6H, q, $J = 7.5$ Hz); $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3), δ in ppm = 172.6 (s), 130.2 (d), 124.3 (d), 68.7 (d), 65.6 (d), 59.9 (t), 43.1 (t), 41.6 (t), 37.8 (q), 37.4 (t), 35.6 (q), 31.7 (t), 27.2 (d), 20.1 (q), 7.1 (q), 4.7 (t); MS-EI (m/z , %): 369 (M^+ , 2), 340 (8), 255 (5), 210 (10), 182 (7), 132 (7), 103 (100), 75 (85); HRMS: found 369,2670 \pm 5 ppm, $\text{C}_{20}\text{H}_{39}\text{NO}_3\text{Si}$ requires 369,2699.

ix) Process for the production of compound 11

[0064]

 $\text{C}_{19}\text{H}_{36}\text{O}_3\text{Si}$

Exact Mass: 340,2434

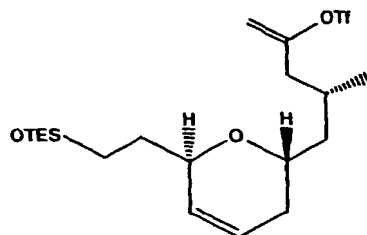
Mol. Wt.: 340,5728

C, 67,01; H, 10,65; O, 14,09; Si, 8,25

[0065] To a solution of amide compound 10 of step ix) (0.2 g, 0.54 mmol) in Et_2O (8 ml) was added a solution of MeLi (0.44 ml, 1.6M in Et_2O , 0.7 mmol) at -78° . The mixture was stirred for 0.5 h and then the cooling bath was removed and the mixture was allowed to warm up to room temperature. The reaction was quenched with saturated solution of NH_4Cl , the organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The crude product was purified by Flash chromatography (hexane : ethyl acetate -5:1) to give compound 11 (0.17 g, 94 %) oil, $[\alpha]_D^{20} = -30.0^\circ$ ($c = 0.40$, CHCl_3); IR (neat) 2954, 2915, 2876, 1717, 1654 1459, 1415, 1360, 1238, 1182, 1090, 940 cm^{-1} ; $^1\text{H-NMR}$ (250 MHz, CDCl_3); δ in ppm = 5.80 (1H, brd, $J = 11.6$ Hz), 5.71 (1H, brd, $J = 11.6$ Hz), 4.35 (1H, m), 3.75 (3H, m), 2.47 (1H, dd, $J = 18.0, 9.0$ Hz), 2.28 (1H, dd, $J = 18.0, 7.5$ Hz), 2.1 (3H, s), 1.8-1.5 (6H, m), 1.20 (1H, m), 0.95 (12H, t, $J = 7.5$ Hz), 0.60 (6H, q, $J = 7.5$ Hz); $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3); δ in ppm = 208.0 (s), 130.3 (d), 124.3 (d), 68.8 (d), 65.4 (d), 59.9 (t), 52.3 (t), 43.0 (d), 37.3 (t), 31.7 (t), 30.3 (q), 26.4 (d), 19.2 (q), 7.1 (q), 4.7 (t); MS-EI (m/z , %): 340 (M^+ , 3), 311 (100), 281 (12), 269 (7), 213 (80), 183 (43), 150 (38), 109 (70), 81 (65); HRMS: found 340,2439 \pm 5 ppm, $\text{C}_{14}\text{H}_{25}\text{NO}_3$ requires 340,2434.

x) Process for the production of compound 12

[0066]

 $C_{20}H_{35}F_3O_5SSi$

Exact Mass: 340,2434

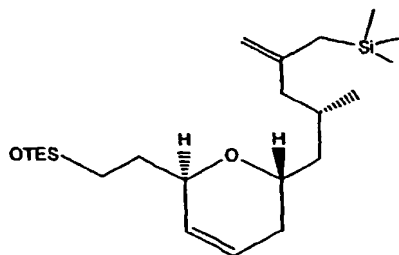
Mol. Wt.: 472,1827

C, 50,82; H, 7,46; F, 12,06; O, 16,93; S, 6,78; Si, 5,94

[0067] To a solution of KHMDS (3 ml, 0.5 M in toluene, 1.5 mmol) was added slowly a solution of ketone compound 11 of step ix) (0.4 g, 1.2 mmol) in THF (5 ml) at -78°C . The mixture was stirred for 1 h and then a solution of PhN(OTf)₂ (0.59 g, 1.6 mmol) in THF (1 ml) was added at same temperature. After being stirred for additional 1 h at -78°C , the cooling bath was removed and the mixture was allowed to warm up to room temperature. The reaction was quenched with saturated solution of Na₂CO₃ (1 ml) and the solution was diluted with toluene (20 ml). The organic phase was washed with saturated solution of Na₂CO₃ (2 X 2 ml), water, brine, dried (Na₂SO₄) and concentrated. The crude product was purified by Flash chromatography (hexane: ethyl acetate: TEA-20:1:0.1) to give compound 12 (0.38 g, 68%) oil, $[\alpha]_D^{20} = -34.8^{\circ}$ ($c = 0.42$, CHCl₃); IR (neat) 2956, 2937, 2877, 1731, 1668, 1574, 1537, 1504, 1460, 1248, 1212, 1182, 1097, 906 cm⁻¹; ¹H-NMR (250 MHz, CDCl₃); δ in ppm = 5.82 (1H, brd, $J = 11.6$ Hz), 5.73 (1H, brd, $J = 11.6$ Hz), 5.17 (1H, d, $J = 3.4$ Hz) 5.05 (1H, d, $J = 3.4$ Hz),

xi) Process for the production of compound 13

[0068]

 $C_{23}H_{46}O_2SSi_2$

Exact Mass: 410,3036

Mol. Wt.: 410,7811

C, 67,25; H, 11,29; O, 7,79; Si, 13,67

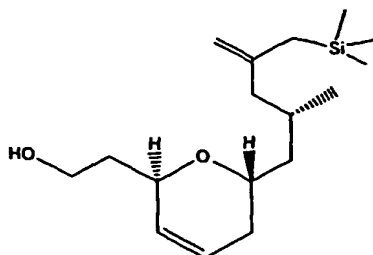
[0069] A slurry of Pd(Ph₃P)₄ (0.018 g, 0.015 mmol) and LiCl (0.03 g, 0.04 mmol) in ether (15 ml) was stirred for 10 min and then a solution of enoltriflate 12 of step x) (0.1 g, 0.2 mmol) in ether (1 ml) was added dropwise. After being stirred for additional 10 min a solution of TMSCH₂MgCl (0.4 ml, 1M in ether, 0.4 mmol) was added at once. After 15 min, the reaction was quenched with saturated solution of Na₂CO₃ (1 ml) and the solution was diluted with toluene (10 ml). The organic phase was washed with water followed by brine, dried (Na₂SO₄) and concentrated. The crude product was purified by Flash chromatography (hexane: ethyl acetate : TEA-25:1:0.1) to give compound 13 (0.084 g, 96%) oil, $[\alpha]_D^{20} = -38.7^{\circ}$ ($c = 0.40$, CHCl₃); IR (neat) 3071, 3032, 2954, 1631, 1418, 1392, 1247, 1180, 1158, 1097, 850 cm⁻¹; ¹H-NMR (250 MHz, CDCl₃); δ in ppm = 5.85 (1H, brd, $J = 11.4$ Hz), 5.71 (1H, brd, $J = 11.4$ Hz), 4.60 (2H, ABq,

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$J=8.3$ Hz), 4.33 (1H, brd, $J=9.3$ Hz), 3.82 (3H, m), 2.0-1.8 (6H, m), 1.7-1.5 (3H, m), 1.10-1.0 (2H, m), 0.92 (9H, t, $J=7.9$ Hz), 0.86 (3H, d, $J=6.6$), 0.65 (6H, q, $J=7.9$ Hz), 0.17 (9H, s); ^{13}C -NMR (62.5 MHz, CDCl_3), δ in ppm = 201.37 (d), 146.4 (s), 128.2 (d), 126.1 (d), 109.2 (t), 68.2 (d), 66.0 (d), 48.3 (t), 47.2 (t), 42.5 (t), 31.4 (t), 27.1 (d), 26.7 (t), 19.7 (q), 0.8 (q); MS-El (m/z , %): 410 (M^+ , 8), 395 (6), 278 (27), 239 (84), 181 (25), 155 (22), 117 (38), 73 (100); HRMS: found 410.3021 \pm 5 ppm, $\text{C}_{23}\text{H}_{46}\text{O}_2\text{Si}_2$ requires 410.3036.

xii) Process for the production of compound 14

[0070]



$\text{C}_{17}\text{H}_{32}\text{O}_2\text{Si}$

Exact Mass: 296,2172

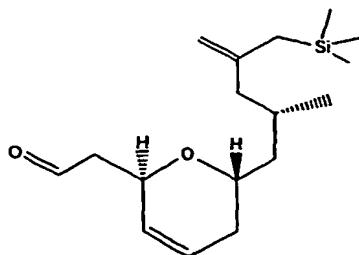
Mol. Wt.: 296,5203

C, 68,86; H, 10,88; O, 10,79; Si, 9,47

[0071] The slurry K_2CO_3 (0.2 g) and compound 13 of step xi) (0.1 g) in methanol (2 ml) was stirred for 12 h at room temperature. The solvent was evaporated and saturated solution of NH_4Cl (1 ml) was added. The mixture was extracted with ethyl acetate (3 X 5 ml). The organic phase was washed with water followed by brine, dried (Na_2SO_4) and concentrated. The crude mixture was purified by Flash chromatography (hexane :ethyl acetate :TEA-10:1:0.1) to give the alcohol 14 (0.07 g, 96%), oil; $[\alpha]_D^{20} = -42.5^\circ$ ($c=0.50$, CHCl_3); IR (neat) 3540, 3071, 3030, 2960, 1631, 1418, 1392, 1180, 1158, 850 cm^{-1} ; ^1H -NMR (250 MHz, CDCl_3); δ in ppm = 5.82 (1H, brd, $J=11.4$ Hz), 5.72 (1H, brd, $J=11.4$ Hz), 4.57 (2H, s), 4.30 (1H, brd, $J=9.3$ Hz), 3.82 (3H, m), 2.0-1.8 (6H, m), 1.7-1.5 (3H, m), 1.10-1.0 (2H, m), 0.91 (3H, d, $J=6.6$), 0.17 (9H, s); ^{13}C -NMR (62.5 MHz, CDCl_3), δ in ppm = 146.0 (s), 130.4 (d), 124.8 (d), 110.0 (t), 69.9 (d), 65.2 (d), 47.3 (t), 43.3 (t), 37.2 (t), 32.0 (t), 27.2 (d), 26.6 (t), 19.6 (q), 4.72 (t), -0.9 (q); HRMS: found 296.2175 \pm 5 ppm, $\text{C}_{17}\text{H}_{32}\text{O}_2\text{Si}$ requires 296.2172.

xiii) Process for the production of compound 15

[0072]



$\text{C}_{17}\text{H}_{30}\text{O}_2\text{Si}$

Exact Mass: 294,2015

Mol. Wt.: 294,5044

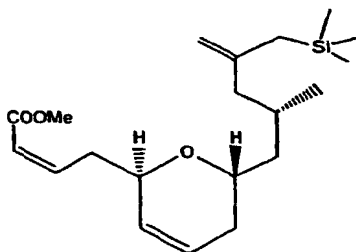
C, 69,33; H, 10,27; O, 10,87; Si, 9,54

[0073] To a mixture of alcohol (0.05 g, 0.17 mmol) and TEA (0.07 ml) in CH_2Cl_2 (1.5 ml) was added a solution of $\text{SO}_3\cdot\text{Py}$ complex (0.08 g, 0.5 mmol) in DMSO (1.5 ml) at 0°C . and stirred for 15 min. The reaction was quenched with

saturated solution of NH_4Cl , and extracted with ethyl acetate (3 X 5 ml). The combined extracts were washed with water followed by brine, dried (Na_2SO_4) and concentrated. Flash chromatography (hexane : ethyl acetate:TEA-15:1: 0.1) of the crude products gave compound **15** (0.044 g, 86%), oil, $[\alpha]_D^{20} = -65.3^\circ$ ($c = 0.68$, CHCl_3); IR (neat) 2952, 2924, 1725, 1647, 1438, 1248, 1216, 1168, 1093 cm^{-1} ; $^1\text{H-NMR}$ (250 MHz, CDCl_3); δ in ppm = 9.81 (1H, dd, $J = 3.1, 1.7$), 5.90 (1H, m), 5.74 (1H, d, $J = 11.9$), 4.80 (1H, m), 4.60 (2H, brs), 3.79 (1H, m), 2.84 (1H, ddd, $J = 16.0, 9.0, 3.0$), 2.60 (1H, ddd, $J = 16.0, 4.6, 1.8$), 2.0-1.8 (5H, m), 1.7-1.5 (2H, m), 1.10 (1H, m), 0.9 (3H, d, $J = 6.4$), 0.04 (9H, s); $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3); δ in ppm = 168.8 (s), 147.7 (d), 146.5 (s), 129.4 (d), 125.4 (d), 120.8 (d), 109.1 (t), 72.3 (d), 65.7 (d), 51.4 (q), 47.3 (t), 42.9 (t), 33.9 (t), 31.7 (t), 27.2 (d), 26.7 (t), 19.7 (q), -0.8 (q); HRMS: found: 294,2010 \pm 5 ppm, $\text{C}_{17}\text{H}_{30}\text{O}_2\text{Si}$ requires 294,2015.

xiv) Process for the production of compound 16

[0074]



$\text{C}_{20}\text{H}_{34}\text{O}_3\text{Si}$

Exact Mass: 350,2277

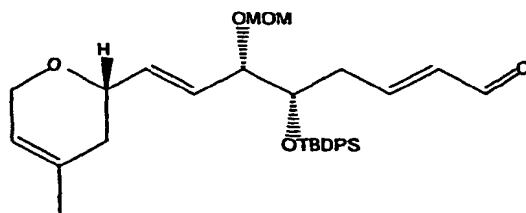
Mol. Wt.: 350,5677

C, 68,52; H, 9,78; O, 13,69; Si, 8,01

[0075] To a mixture of $(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(\text{O})\text{CH}_2\text{COOMe}$ (0.1 g, 0.3 mmol) and 18-crown-6 (0.43 g, 1.6 mmol) in THF (2 ml) was added KHMDS (0.68 ml, 0.5 M in Tol, 0.3 mmol) at -78°C . After 45 min a solution of aldehyde compound **15** (0.08 g, 0.28 mmol) in THF (1 ml) was added dropwise and the mixture was stirred additional 45 min. The reaction was quenched with saturated solution of NH_4Cl and extracted with ethyl acetate, (3 X 5 ml). The combined extracts were washed with water followed by brine, dried (Na_2SO_4) and concentrated. Flash chromatography of the crude products (ethyl acetate : hexane 1:1) gave pure (Z)- isomer (0.085 g, 90%) as a colourless oil, $[\alpha]_D^{20} = -68.6^\circ$ ($c = 0.23$, CHCl_3); IR (neat) 2952, 2924, 1725, 1647, 1438, 1248, 1216, 1168, 1093 cm^{-1} ; $^1\text{H-NMR}$ (250 MHz, CDCl_3); δ in ppm = 6.41 (1H, ddd, $J = 11.6, 7.3, 4.3$), 5.85 (2H, m), 5.75 (1H, brd, $J = 11.4$), 4.58 (2H, brs), 4.30 (1H, brs), 3.90 (1H, m), 3.81 (3H, s), 2.98 (2H, m), 2.0-1.8 (5H, m), 1.7-1.5 (2H, m), 1.10 (1H, m), 0.86 (3H, d, $J = 6.6$), 0.17 (3H, s); $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3); δ in ppm = 168.8 (s), 147.7 (d), 146.5 (s), 129.4 (d), 125.4 (d), 120.8 (d), 109.1 (t), 72.3 (d), 65.7 (d), 51.4 (q), 47.3 (t), 42.9 (t), 33.9 (t), 31.7 (t), 27.2 (d), 26.7 (t), 19.7 (q), -0.8 (q); MS-EI (m/z , %): 350 (M^+ , 4), 335 (3), 251 (55), 182 (38), 109 (13), 73 (100); HRMS: found: 350,2273 \pm 5 ppm, $\text{C}_{20}\text{H}_{34}\text{O}_3\text{Si}$ requires 350,2260.

xv) Process for the production of compound 2a

[0076]



$\text{C}_{32}\text{H}_{42}\text{O}_5\text{Si}$

Exact Mass: 534,2802

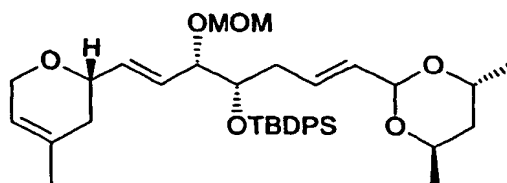
Mol. Wt.: 534,7584

C, 71,87; H, 7,92; O, 14,96; Si, 5,25

[0077] A solution of alcohol compound **1a** (0.53 g, 1 mmol) in dry CH_2Cl_2 (2 ml) was added dropwise to a slurry of Dess-Martin periodinane (1.3 g, 5 mmol) and NaHCO_3 (2 g) in CH_2Cl_2 (20 ml). The mixture was stirred at room temperature for 15 min, then subjected directly to SiO_2 Flash chromatography (hexane-ethyl acetate : 5:1) to yield compound **2a** (0.500g, 95%) as a colourless liquid, $[\alpha]_D^{20} = -9.7^\circ$ ($c = 0.75$, CHCl_3); IR (neat) 29312, 2924, 1692, 1427, 1106, 1033, 977, 741 cm^{-1} ; $^1\text{H-NMR}$ (250 MHz, CDCl_3); δ in ppm = 9.28 (1H, d, $J = 7.9$ Hz), 7.71 (4H, m), 7.43 (6H, m), 6.64 (1H, ddd, $J = 15.4, 7.4, 7.4$ Hz), 5.94 (1H, dd, $J = 15.4, 7.9$ Hz), 5.81 (2H, m), 5.45 (1H, brs), 4.54 (1H, d, $J = 6.6$ Hz), 4.44 (1H, d, $J = 6.6$ Hz), 4.13 (5H, m), 3.20 (3H, s), 2.47 (2H, m), 1.75 (3H, brs), 1.10 (9H, s); $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3), δ in ppm = 194.3 (d), 156.2 (d), 136.4 (d), 136.3 (d), 135.1 (d), 134.7 (s), 131.7 (s), 128.1 (d), 126.6 (d), 120.2 (d), 95.1 (t), 78.8 (d), 65.9 (t), 55.9 (d), 36.3 (t), 36.0 (t), 27.4 (q), 23.3 (q), 21.4 (s); MS-EI (m/z , %): 534. (M^+ , 0.1), 477 ($\text{M}^+ - t\text{-Bu}$, 0.43), 415 (6), 337 (38), 109 (15), 267 (12), 233 (30), 199 (100), 135 (88), 91(30); HRMS: found: 477,2079 \pm 5 ppm, $\text{C}_{28}\text{H}_{33}\text{O}_5\text{Si}$ requires 477,2097 ($\text{M}^+ - t\text{-Bu}$).

xvi) Process for the production of compound **3a**

[0078]

 $\text{C}_{37}\text{H}_{52}\text{O}_6\text{Si}$

Exact Mass: 620,3533

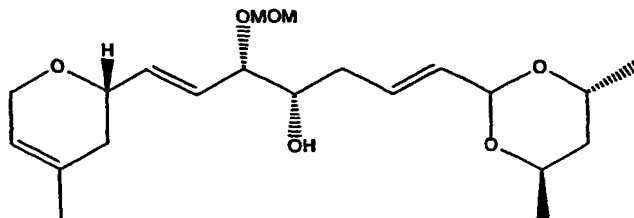
Mol. Wt.: 620,8907

C, 71,57; H, 8,44; O, 15,46; Si, 4,52

[0079] To a solution of compound **2a** from step **xv** (0.530 g, 1 mmol) and (R, R)-(-)-2,4-pentanediol (0.16 g, 1.6 mmol) in dry toluene (20 ml) was added Montmorillonit K-10 (20 mg) and the mixture was slowly rotated on a rotavapour at 80 mbars and 40°C . The reaction was monitored by TLC and the volume of the solvent was kept constant by addition of additional portions of solvent. At the end the reaction mixture was filtered through a short pad of SiO_2 (hexane : ethyl acetate : TEA - 5:1:0.1) to give compound **3a** (0.55 g, 89%), oil, $[\alpha]_D^{20} = +14.3^\circ$ ($c = 0.18$, CHCl_3); IR (neat) 2940, 2925, 1427, 1130, 1125, 1106, 1033, 977, 741 cm^{-1} ; $^1\text{H-NMR}$ (250 MHz, CDCl_3); δ in ppm = 7.71 (4H, m), 7.43 (6H, m), 5.78 (3H, m), 5.40 (2H, m), 5.19 (1H, d, $J = 5.0$ Hz), 4.54 (1H, d, $J = 6.6$ Hz), 4.40 (1H, d, $J = 6.6$ Hz), 4.32 (1H, ddd, $J = 13.2, 6.8, 6.6$ Hz), 4.20 (2H, brs), 4.1-3.8 (4H, m), 3.20 (3H, s), 2.4-1.8 (5H, m), 1.83 (3H, brs), 1.4 (3H, d, $J = 7.2$ Hz), 1.3 (2H, m), 1.24 (3H, d, $J = 6.4$ Hz), 1.10 (9H, s); $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3), δ in ppm = 136.6 (d), 136.5 (d), 136.4 (d), 135.1 (d), 134.7 (s), 133.8 (s), 132.2 (d), 132.0 (s), 129.6 (d), 128.1 (d), 128.0 (d), 127.9 (d), 120.1 (d), 93.8 (t), 92.5 (d), 78.6 (d), 76.2 (d), 75.2 (d), 68.4 (d), 68.3 (d), 65.9 (t), 55.9 (d), 35.9 (t), 35.7 (t), 27.5 (q), 23.4 (q), 22.3 (q), 19.8 (t), 19.6 (s), 17.6 (q); MS-EI (m/z , %): 620 (M^+ , 3), 563 (15), 423 (60), 337 (18), 275 (45), 199 (100), 135 (94); HRMS: found: 620,3541 \pm 5 ppm, $\text{C}_{37}\text{H}_{52}\text{O}_6\text{Si}$ requires 620,3533.

xvii) Process for the production of compound 4a

[0080]

 $C_{21}H_{34}O_6$

Exact Mass: 382,2355

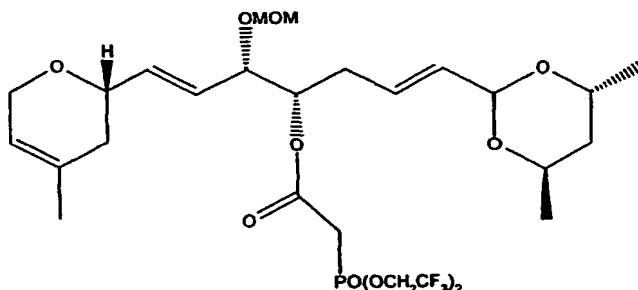
Mol. Wt.: 382,4911

C, 65,94; H, 8,96; O, 25,10

[0081] A solution of compound 3a of step xvi) (0.76, 1.2 mmol) and TBAF (1M, 3 ml) in THF (5 ml) was kept for 24 h at room temperature. The reaction was quenched with saturated solution of NH_4Cl . The organic phase was extracted with ethyl acetate, (3 X 5 ml). The combined extracts were washed with water followed by brine, dried (Na_2SO_4) and concentrated. Flash chromatography of the crude product (hexane : ethyl acetate : 1:2) gave alcohol compound 4a as a colourless oil (0.45 g, 96%); $[\alpha]_D^{20} = +14.3^\circ$ (c=0.08 in $CHCl_3$); IR (neat), 3650, 3467, 2971, 1679, 1448, 1377, 1288, 1240, 1153, 1137, 971 cm^{-1} ; 1H -NMR (250 MHz, $CDCl_3$); δ in ppm = 5.94 (1H, ddd, $J=15.0, 7.3, 6.4$ Hz), 5.82 (1H, dd, $J=15.7, 5.3$ Hz), 5.59 (2H, m), 5.39 (1H, brs), 5.25 (1H, d, $J=5.0$ Hz), 4.69 (1H, d, $J=6.6$ Hz), 4.54 (1H, d, $J=6.6$ Hz), 4.30 (1H, ddd, $J=13.2, 6.8, 6.6$ Hz), 4.19 (2H, m), 4.02 (2H, m), 3.89 (1H, dd, $J=7.4, 6.7$ Hz), 3.61 (1H, m), 3.35 (3H, s), 2.4-1.8 (5H, m), 1.61 (3H, brs), 1.36 (3H, d, $J=7.1$ Hz), 1.31 (1H, m), 1.19 (3H, d, $J=6.2$ Hz); ^{13}C -NMR (62.5 MHz, $CDCl_3$), δ in ppm = 136.6 (d), 131.6 (d), 131.3 (s), 130.6 (d), 127.1 (d), 120.0 (d), 94.4 (t), 93.6 (d), 80.0 (d), 73.3 (d), 68.4 (d), 67.8 (d), 65.9 (t), 56.0 (d), 37.0 (t), 36.1 (t), 36.0 (t), 23.2 (q), 22.2 (q), 17.5 (q); MS-EI (m/z, %): 620 (M^+ , 3), 563 (15), 423 (60), 337 (18), 275 (45), 199 (100), 135 (94), HRMS: found: 620,3541 \pm 5 ppm, $C_{21}H_{34}O_6$ requires 620,3533

xviii) Process for the production of compound 5a

[0082]

 $C_{27}H_{39}F_6O_{10}P$

Exact Mass: 668,2185

Mol. Wt.: 668,5567

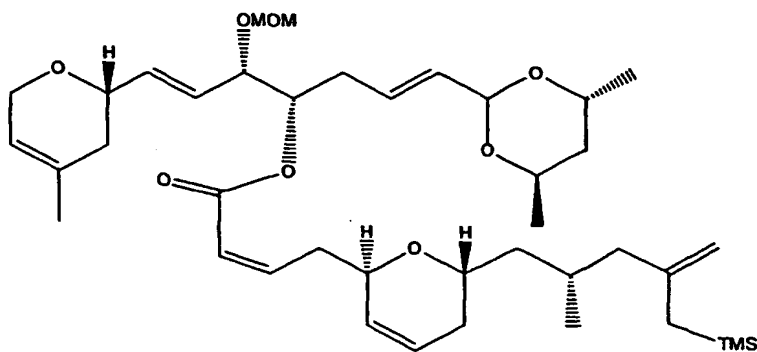
C, 48,51; H, 5,88; F, 17,05; O, 23,93; P, 4,63

[0083] To a solution of alcohol compound 4a of step xvii) (0.76 g, 2 mmol) and DMAP (0.6 g, 3 mmol) in dry CH_2Cl_2 (10 ml) was added slowly a solution of $(CF_3CH_2O)_2P(O)CH_2COCl$ (1.07 g, 1.6 eqv) in CH_2Cl_2 at $-78^\circ C$. After 15 min pyridine (0.3 ml) was added at the same temperature and the mixture was allowed to warm up slowly to room temper-

ature (approximately 2 h). The reaction was quenched with saturated solution of NaHCO_3 . The organic phase was extracted with CH_2Cl_2 (3 X 5 ml). The combined extracts were washed with water followed by brine, dried (Na_2SO_4) and concentrated. Flash chromatography of the crude product (hexane: ethyl acetate: 1:1) gave compound **5a** as a colourless oil (0.45 g, 96%); $[\alpha]_D^{20} = -48^\circ$ ($c=0.25$ in CHCl_3); IR (neat), 2974, 1740, 1269, 1173, 1104, 964 cm^{-1} ; $^1\text{H-NMR}$ (250 MHz, CDCl_3); δ in ppm = 5.87 (1H, dd $J=15.7, 5.3$ Hz), 5.76 (1H, t, $J=6.6$ Hz), 5.60 (2H, m), 5.43 (1H, brs), 5.24 (1H, d, $J=5.0$ Hz), 5.07 (1H, ddd $J=10.0, 8.3, 5.1$ Hz), 4.69 (1H, d, $J=6.9$ Hz), 4.54 (1H, d, $J=6.9$ Hz), 4.47 (5H, m), 4.32 (1H, ddd $J=13.2, 6.8, 1.5$ Hz), 4.10 (3H, m), 4.02 (2H, m), 3.37 (3H, s), 3.24 (1H, dd, $J=16.2, 21.0$ Hz), 3.18 (1H, dd, $J=16.2, 20.4$ Hz), 2.5-2.2 (2H, m), 2.1-1.7 (4H, m), 1.71 (3H, brs), 1.38 (3H, d, $J=7.1$ Hz), 1.30 (1H, m), 1.22 (3H, d, $J=6.8$ Hz); $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3), δ in ppm = 160.4 (s), 137. (d), 131.6 (d), 132.1 (d), 131.6 (s), 129.0 (d), 125.8 (d), 120.1 (d), 94.3 (t), 93.3 (d), 76.6 (d), 76.5 (d), 73.3 (d), 68.5 (d), 67.9 (d), 65.9 (t), 63.3 (t), 62.5 (t), 56.1 (d), 37.0 (t), 36.0 (t), 35.4 (t), 33.7 (t), 33.1 (t), 23.2 (q), 22.2 (q), 22.2 (q), 17.5 (q); MS-EI (m/z , %): 668 (M^+ , 6), 623 (8), 521 (5), 469 (6), 369 (15), 287 (85), 217 (30), 115 (80); HRMS: found: 628,2201 \pm 5 ppm, $\text{C}_{27}\text{H}_{39}\text{F}_6\text{O}_{10}\text{P}$ requires 668,2185

xix) Process for the production of compound 6a

[0084]



$\text{C}_{40}\text{H}_{64}\text{O}_8\text{Si}$

Exact Mass: 700.4370

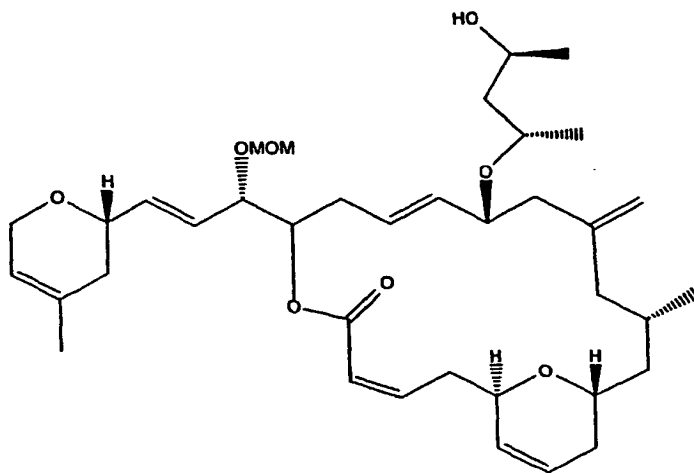
Mol. Wt.: 701.0169

C, 68.53; H, 9.20; O, 18.26; P, 4.01

[0085] To a mixture of compound **5a** of step xviii) (0.1 g, 0.15 mmol) and 18-crown-6 (0.21 g, 0.8 mmol) in THF (2 ml) was added KHMDS (0.29 ml, 0.5 M in toluene, 0.15 mmol) at -78°C . After 45 min a solution of aldehyde compound **15** (0.052 g, 0.18 mmol) in THF (1 ml) was added dropwise and the mixture was stirred an additional 45 min. The reaction was quenched with saturated solution of NH_4Cl and extracted with ethyl acetate, (3 X 5 ml). The combined extracts were washed with water followed by brine, dried (Na_2SO_4) and concentrated. Flash chromatography of the crude product (hexane : ethyl acetate - 1:1) gave pure (Z)- isomer compound **6a** (0.089g, 85%) as a colourless oil; $[\alpha]_D^{20} = -28^\circ$ ($c=0.2$ in CHCl_3); IR (neat), 2928, 1719, 1680, 1640, 1560, 1376, 1274, 1164, 1099, 997 cm^{-1} ; $^1\text{H-NMR}$ (600 MHz, CDCl_3); δ in ppm = 6.45 (ddd, $J=11.5, 7.6, 6.5$ Hz), 5.91 (1H, dt, $J=11.5, 1.9$ Hz), 5.82 (2H, m), 5.72 (1H, dq, $J=9.0, 2.3$ Hz), 5.59 (2H, m), 5.40 (1H, brs), 5.24 (1H, d, $J=5.2$ Hz), 5.06 (1H, ddd, $J=10.6, 8.5, 5.1$ Hz), 4.69 (1H, d, $J=6.8$ Hz), 4.59 (1H, bs), 4.58 (1H, d, $J=6.8$ Hz), 4.56 (1H, brs), 4.32 (1H, ddd $J=13.4, 6.7, 6.7$ Hz), 4.28 (1H, m), 4.19 (3H, m), 4.03 (2H, m), 3.81 (1H, m), 3.37 (3H, s), 3.0 (1H, m), 2.93 (1H, m), 2.51 (1H, m), 2.36 (1H, m), 2.1-1.8 (9H, m), 1.71 (3H, brs), 1.67 (2H, m), 1.52 (2H, m), 1.38 (3H, d, $J=6.9$ Hz), 1.35 (1H, brd, $J=13.3$ Hz), 1.23 (3H, d, $J=6.1$ Hz), 1.1 (1H, m), 0.87 (3H, d, $J=6.4$ Hz), 0.3 (9H, s); $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3), δ in ppm = 165.5 (s), 147.9 (d), 146.2 (s), 131.6 (s), 131.3 (d), 129.9 (d), 129.4 (d), 126.4 (d), 125.3 (d), 120.9 (d), 120.1 (d), 109.1 (t), 94.4 (t), 93.5 (d), 76.6 (d), 73.8 (d), 73.5 (d), 72.3 (d), 68.5 (d), 67.8 (d), 65.9 (t), 65.5 (d), 47.3 (t), 42.8 (t), 37.1 (t), 36.0 (t), 34.0 (t), 33.6 (t), 31.7 (t), 27.1 (d), 26.7 (t), 23.3 (q), 22.2 (q), 19.7 (q), 17.6 (q), 0.8 (q); MS-EI (m/z , %): 700 (M^+ , 4), 613 (8), 503 (4), 365 (95), 303 (12), 251 (85), 161 (35), 115 (55); HRMS: found 700.4395, requires for $\text{C}_{40}\text{H}_{64}\text{O}_8\text{Si}$ 700.4370.

xx) Process for the production of compound 7a

[0086]

 $C_{37}H_{56}O_8$

Exact Mass: 628,3975

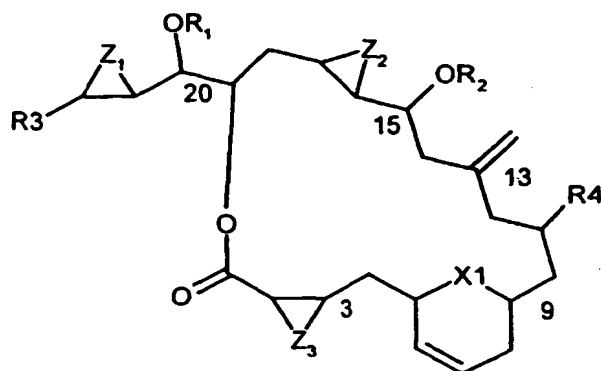
Mol. Wt.: 628,8357

C, 70,67; H, 8,98; O, 20,35

[0087] To a solution of $EtAlCl_2$ (0.1 ml, 1M in CH_2Cl_2 , 0.1 mmol) in 15 ml CH_2Cl_2 was added slowly (syringe pump), a solution of compound 6a of step xix) (0.04 g., 0.05 mmol) in CH_2Cl_2 (1ml) at $-50^\circ C$. After the addition was finished, the reaction mixture was allowed to warm up to $^\circ C$. The reaction was quenched with buffer (pH = 7, 2 ml) and stirred for 2 h. The organic phase was separated and the water phase was extracted with CH_2Cl_2 , (3 X 5 ml). The combined extracts were washed with water followed by brine, dried (Na_2SO_4) and concentrated. Flash chromatography of the crude product (hexane: ethyl acetate: 1:1) gave compound 7a as a colourless oil (0.031 g, 85%); $[\alpha]_D^{20} = -31^\circ$ (c=0.1 in $CHCl_3$); IR (neat), 3500, 2928, 17290, 1682, 1638, 1510, 1376, 1164, 990 cm^{-1} ; 1H -NMR (6.31 (ddd, $J=11.5, 10.0, 5.3$ Hz), 5.91 (1H, d, $J=6.9$ Hz), 5.84 (2H, m), 5.71 (1H, dd, $J=9.9, 1.9$ Hz), 5.62 (1H, m), 5.58 (1H, ddd, $J=7.2, 2.0, 1.3$ Hz), 5.47 (dd, $J=15.5, 8.0$ Hz), 5.41 (1H, brs), 5.09 (1H, dd $J=12.8, 6.4$ Hz), 4.79 (1H, brs), 4.76 (1H, brs), 4.67 (1H, d, $J=6.8$ Hz), 4.55 (1H, bs), 4.24 (1H, brs), 4.11 (6H, m), 3.96 (1H, ddd $J=8.3, 8.0, 4.7$ Hz), 3.83 (2H, m), 3.62 (1H, m), 3.34 (3H, s), 3.0 (1H, m), 2.36 (2H, t, $J=6.9$ Hz), 2.3-2.0 (5H, m), 1.87 (2H, m), 1.74 (2H, m), 1.60 (2H, m), 1.56 (3H, s), 1.52 (1H, ddd $J=14.5, 6.3, 2.2$ Hz), 1.26 (3H, d, $J=6.2$ Hz), 1.12 (3H, d, $J=6.1$ Hz), 0.85 (3H, d, $J=6.2$ Hz); ^{13}C -NMR (62.5 MHz, $CDCl_3$), δ in ppm = 165.2 (s), 146.9 (d), 144.3 (s), 136.1 (d), 134.2 (d), 131.4 (s), 128.5 (d), 128.4 (d), 126.0 (d), 125.1 (d), 121.7 (d), 119.8 (d), 115.6 (d), 112.9 (t), 94.0 (t), 75.3 (d), 74.0 (d), 73.5 (d), 73.3 (d), 71.9 (d), 69.8 (d), 67.2 (d), 65.9 (t), 64.3 (d), 55.7 (d), 44.8 (d), 44.7 (t), 43.0 (t), 42.8 (t), 38.8 (t), 36.2 (t), 35.9 (t), 34.4 (t), 33.0 (t), 31. (t), 31.4 (t), 29.8 (t), 28.3 (d), 24.4 (t), 23.5 (q), 23.0 (q), 22.7 (t), 20.0 (q), 18.3 (q), 14.2 (q); HRMS: found: 628.3930 $^+$. 5 ppm, $C_{37}H_{56}O_8$ requires 628.3975.

Claims

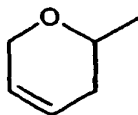
1. Laulimalid derivatives of general formula I



(I),

in which

- R^1 and R^2 independently from each other have the meaning of hydrogen, α -alkyl, β -alkyl, methylmethylether, alkyl optionally substituted with hydroxy, paramethoxybenzyl, benzyl, or a protecting group,
- R^3 has the meaning of a five or six membered, optionally substituted aryl or heteroaryl ring, or a five or six membered optionally substituted and optionally partially saturated cycloalkyl ring, which can be interrupted by oxygen, sulphur or the group $=NR^5$,
- R^4 has the meaning of α -alkyl, β -alkyl, aryl or trifluoromethyl,
- X_1 has the meaning of oxygen, sulphur or the group $=NR^5$, in which
- R^5 has the meaning of hydrogen, alkyl, cycloalkyl or aryl,
- Z_1 has the meaning of a (Z)- or (E)-double bond, triple bond, or has the meaning of oxygen, sulphur or the group $-CH_2-$, $-CH_2-CH_2-$, $=C(OH)_2$, $=C(halogen)(OH)$, $=C(OH)NR^6$ or $=NR^7$,
- Z_2 has the meaning of a (Z)- or (E)-double bond, triple bond, or has the meaning of oxygen (α - or β -epoxide), sulphur or the group $-CH_2-$, $-CH_2-CH_2-$, $=C(OH)_2$, $=C(halogen)(OH)$, $=C(OH)NR^6$ or $=NR^7$,
- Z_3 has the meaning of a (Z) or (E)-double bond,
- R^6 has the meaning of alkyl, cycloalkyl or aryl, and
- R^7 has the meaning of hydrogen, alkyl, cycloalkyl or aryl,

and the optical isomers and salts thereof, except of those compounds in which R^3 stands for the cycloalkyl ring

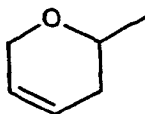
and X_1 has the meaning of oxygen, R^1 has the meaning of α -methyl, Z_1 has the meaning of a (E)-double bond, Z_2 has the meaning of β -epoxide if Z_3 has the meaning of a (Z)-double bond.

2. Lulimalid derivatives of general formula I, according to claim 1, in which

- R^1 and R^2 independently from each other have the meaning of hydrogen, α -C₁-C₆-alkyl, β -C₁-C₆-alkyl, methylmethylether, C₁-C₆-alkyl optionally substituted with hydroxy, paramethoxybenzyl, benzyl, or a silyl protecting group, or an acetyl, benzyl, carbamate or carbonate protecting group,
- R^3 has the meaning of a five or six membered, optionally substituted aryl or heteroaryl ring, or a five or six membered optionally substituted and optionally partially saturated C₃-C₇-cycloalkyl ring, which

- can be interrupted by oxygen, sulphur or the group =NR⁵,
 R⁴ has the meaning of α -C₁-C₆-alkyl, β -C₁-C₆-alkyl, aryl or trifluoromethyl,
 X₁ has the meaning of oxygen, sulphur or the group =NR⁵, in which
 R⁵ has the meaning of hydrogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl or aryl,
 5 Z₁ has the meaning of a (Z)- or (E)-double bond, triple bond, or has the meaning of oxygen, sulphur or the group -CH₂-, -CH₂-CH₂-, =C(OH)₂, =C(halogen)(OH), =C(OH)NR⁶ or =NR⁷,
 Z₂ has the meaning of a (Z)- or (E)-double bond, triple bond, or has the meaning of oxygen (α - or β -epoxide), sulphur or the group -CH₂-, -CH₂-CH₂-, =C(OH)₂, =C(halogene)(OH), =C(OH)NR⁶ or =NR⁷,
 10 Z₃ has the meaning of a (Z) or (E)-double bond,
 R⁶ has the meaning of C₁-C₆-alkyl, C₃-C₇-cycloalkyl or aryl, and
 R⁷ has the meaning of hydrogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl or aryl,

and the optical isomers and salts thereof, except of those compounds in which R³ stands for the cycloalkyl ring

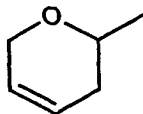


and X₁ has the meaning of oxygen, R¹ has the meaning of α -methyl, Z₁ has the meaning of a (E)-double bond, Z₂ has the meaning of β -epoxide if Z₃ has the meaning of a (Z)-double bond.

3. Laulimalid derivatives of general formula I, according to claims 1 and 2, in which

- R¹ and R² independently from each other have the meaning of hydrogen, α -C₁-C₆-alkyl, β -C₁-C₆-alkyl, methylmethylether, C₁-C₆-alkyl optionally substituted with hydroxy, paramethyloxybenzyl, benzyl, or a silyl protecting group, or an acetyl, benzyl, carbamate or carbonate protecting group,
 30 R³ has the meaning of optionally substituted phenyl, biphenyl, naphthyl, thiophene, furan, oxazole, thiazole, imidazole, pyrazole, pyridin, pyrimidine, triazine, quinolin, isoquinolin or benzo derivatives thereof, or a five or six membered optionally substituted and optionally partially saturated C₃-C₇-cycloalkyl ring, which can be interrupted by oxygen, sulphur or the group =NR⁵,
 R⁴ has the meaning of α -C₁-C₆-alkyl, β -C₁-C₆-alkyl, phenyl, biphenyl, naphthyl, or trifluoromethyl,
 35 X₁ has the meaning of oxygen, sulphur or the group =NR⁵, in which
 R⁵ has the meaning of hydrogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, phenyl, biphenyl or naphthyl,
 Z₁ has the meaning of a (Z)- or (E)-double bond, triple bond, or has the meaning of oxygen, sulphur or the group -CH₂-, -CH₂-CH₂-, =C(OH)₂, =C(halogen)(OH), =C(OH)NR⁶ or =NR⁷,
 40 Z₂ has the meaning of a (Z)- or (E)-double bond, triple bond, or has the meaning of oxygen (α - or β -epoxide), sulphur or the group -CH₂-, -CH₂-CH₂-, =C(OH)₂, =C(halogene)(OH), =C(OH)NR⁶ or =NR⁷,
 Z₃ has the meaning of a (Z) or (E)-double bond,
 R⁶ has the meaning of C₁-C₆-alkyl, C₃-C₇-cycloalkyl, phenyl, biphenyl or naphthyl, and
 45 R⁷ has the meaning of hydrogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, phenyl, biphenyl or naphthyl,

and the optical isomers and salts thereof, except of those compounds in which R³ stands for the cycloalkyl ring

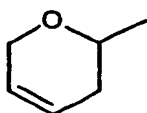


X₁ has the meaning of oxygen, R¹ has the meaning of α -methyl, Z₁ has the meaning of a (E)-double bond, Z₂ has the meaning of β -epoxide if Z₃ has the meaning of a (Z)-double bond.

4. Laulimalid derivatives of general formula I, according to claims 1 to 3, in which

- R¹ and R² independently from each other have the meaning of hydrogen, α -C₁-C₆-alkyl, β -C₁-C₆-alkyl, methylmethylether, C₁-C₆-alkyl optionally substituted with hydroxy, paramethyloxybenzyl, benzyl, or a silyl protecting group, or an acetyl, benzyl, carbamate or carbonate protecting group,
- R³ has the meaning of optionally substituted phenyl, biphenyl, naphthyl, thiophene, furan, oxazole, thiazole, imidazole, pyrazole, pyridin, pyrimidine, triazine, quinolin, isoquinolin or benzo derivatives thereof, or a five or six membered optionally substituted and optionally partially saturated C₃-C₇-cycloalkyl ring, which can be interrupted by oxygen, sulphur or the group =NR⁵,
- R⁴ has the meaning of α -C₁-C₆-alkyl, β -C₁-C₆-alkyl, phenyl, biphenyl, naphthyl, or trifluoromethyl,
- X₁ has the meaning of oxygen,
- Z₁ has the meaning of a (Z)- or (E)-double bond, or has the meaning of oxygen,
- Z₂ has the meaning of a (Z)- or (E)-double bond, or has the meaning of oxygen (α - or β -epoxide) and
- Z₃ has the meaning of a (Z) or (E)-double bond,

and the optical isomers and salts thereof, except of those compounds in which R³ stands for the cycloalkyl ring

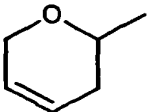


X₁ has the meaning of oxygen, R¹ has the meaning of α -methyl, Z₁ has the meaning of a (E)-double bond, Z₂ has the meaning of β -epoxide if Z₃ has the meaning of a (Z)-double bond.

5. Laulimalid derivatives of general formula I, according to claims 1 to 4, in which

- R¹ and R² independently from each other have the meaning of hydrogen, α -C₁-C₆-alkyl, β -C₁-C₆-alkyl, methylmethylether, C₁-C₆-alkyl optionally substituted with hydroxy, paramethyloxybenzyl, benzyl, or a silyl protecting group, or an acetyl, benzyl, carbamate or carbonate protecting group,
- R³ has the meaning of optionally substituted phenyl, 1,3-thiazoles or 2- and 3-pyridyl, or a six membered optionally substituted and optionally partially saturated cyclohexyl ring, which can be interrupted by oxygen,
- R⁴ has the meaning of α -C₁-C₆-alkyl, β -C₁-C₆-alkyl, phenyl, biphenyl, naphthyl, or trifluoromethyl,
- X₁ has the meaning of oxygen,
- Z₁ has the meaning of a (Z)- or (E)-double bond, or has the meaning of oxygen,
- Z₂ has the meaning of a (Z)- or (E)-double bond, or has the meaning of oxygen (α - or β -epoxide) and
- Z₃ has the meaning of a (Z) or (E)-double bond,

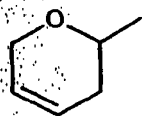
and the optical isomers and salts thereof, except of those compounds in which R³ stands for the cycloalkyl ring



X₁ has the meaning of oxygen, R¹ has the meaning of α -methyl, Z₁ has the meaning of a (E)-double bond, Z₂ has the meaning of β -epoxide if Z₃ has the meaning of a (Z)-double bond.

6. Laulimalid derivatives of general formula I, according to claims 1 to 5, in which

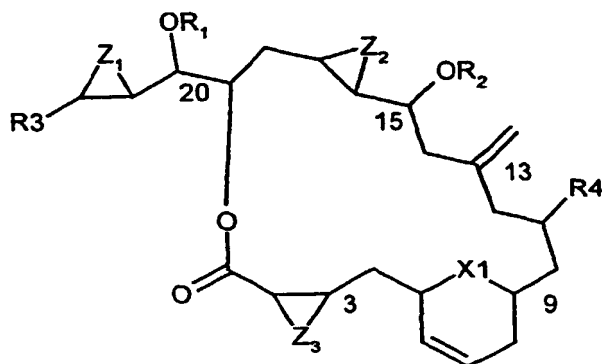
- R¹ and R² independently from each other have the meaning of hydrogen, α -C₁-C₆-alkyl, β -C₁-C₆-alkyl, methylmethylether, C₁-C₆-alkyl optionally substituted with hydroxy, paramethyloxybenzyl, benzyl, or a silyl protecting group, or an acetyl, benzyl, carbamate or carbonate protecting group,
- R³ has the meaning of optionally substituted phenyl, 1,3-thiazoles, 2- and 3-pyridyl or the group



which is substituted with methyl,
 has the meaning of α -C₁-C₆-alkyl, β -C₁-C₆-alkyl, phenyl, biphenyl, naphthyl, or trifluoromethyl,
 has the meaning of oxygen,
 has the meaning of a (Z)- or (E)-double bond,
 has the meaning of a (Z)- or (E)-double bond, and
 has the meaning of a (Z) or (E)-double bond,

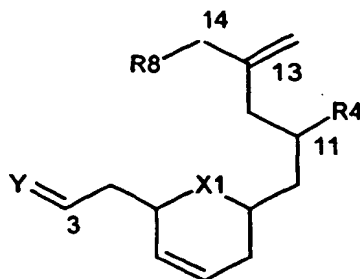
and the optical isomers and salts thereof.

7. Process for the production of laulimalide and laulimalide derivatives of general formula I



(I),

in which
 R¹, R², R³, R⁴, X₁, Z₁, Z₂ and Z₃ have the meaning as defined in claims 1 to 6, **characterised in** by reacting a
 compound of general formula II

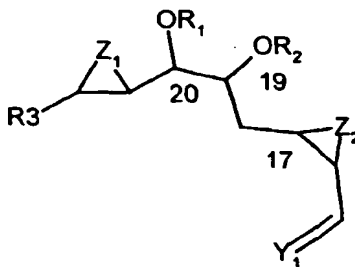


(II),

in which

- R^4 and X_1 have the meaning defined under formula I, and
 R^8 has the meaning of hydrogen, trimethylsilyl, or the group MHal, wherein
M has the meaning of Mg, Li, Ti, Ge or In, and
Y has the meaning of oxygen or the group =CH(OH), (Z) or (E)-CH-COOH, (Z) or (E)-CH-COOR⁹
or (Z) or (E)-CHHal, in which
 R^9 has the meaning of hydrogen, alkyl, cycloalkyl or aryl,

with a compound of general formula III

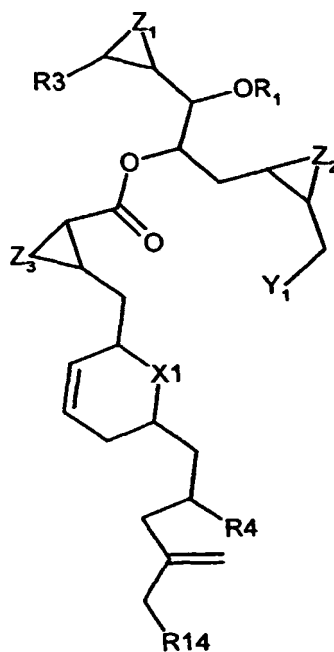


(III),

in which

- R^1 , R^3 , Z_1 und Z_2 have the meaning defined under formula I, and
 R^2 has the meaning of hydrogen, methylmethylether, paramethoxybenzyl, benzyl, or a protecting group, or a group -COCH₂B, wherein
B has the meaning of the group -SiR¹⁰, -SeR¹¹, -Se(O)R¹¹, -TeR¹¹, -PO(OR¹¹)₃ or -P(O)(OCH₂CR¹⁰)₂, in which
 R^{10} has the meaning of alkyl, aryl, alkenyl, or the group -CF₃, or -CH₂OR¹¹, in which
 R^{11} has the meaning of hydrogen, alkyl, cycloalkyl or aryl, and
 Y_1 has the meaning of oxygen, or an alkyl acetal of the group -CH(OR¹²)₂, or a five membered O,O; N,O; O,S; or S,S; cyclic acetal, or six membered O,O; N,O; O,S; or S,S; cyclic acetal, and
 R^{12} has the meaning of alkyl,

to form an intermediate of general formula IV



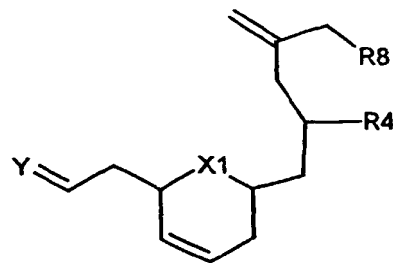
(IV),

in which

R¹, R³, R⁴, X₁ and Z₁-Z₃ have the meaning defined under formula I, and
 Y₁ has the meaning defined under formula III, and
 R¹⁴ has the meaning of hydrogen, halogen, trimethylsilyl, or the group MHal, wherein
 M has the meaning of Mg, Li, Ti, Ge or In,

which is cyclidized to the compounds of general formula I.

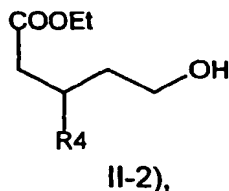
8. Process for the production of intermediates of general formula II,



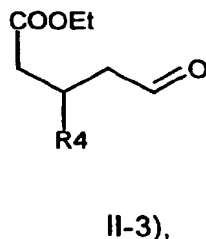
II),

in which R^4 and X_1 have the meaning as defined under formula I, and R^6 has the meaning of hydrogen, trimethylsilyl, or the group MHal, wherein M has the meaning of Mg, Li, Ti, Ge or In, and Y has the meaning of oxygen or the group $=CH(OH)$, (Z) or (E)- $CH-COOH$, (Z) or (E)- $=CH-COOR^9$ or (Z) or (E)- $CHHal$, in which R^9 has the meaning of hydrogen, alkyl, cycloalkyl or aryl, characterized in by reacting

a) an alcohol compound of general formula II-2)

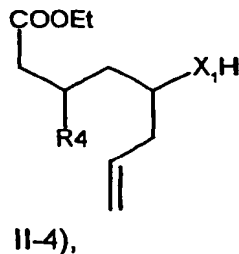


in which R^4 has the meaning as defined under formula I, in a suitable solvent together with a suitable oxidant to give an aldehyde compound of general formula II-3)



in which R^4 has the meaning as defined under formula I,

b) reacting aldehyde compound of general formula II-3) in a suitable solvent with a suitable alkylating agent to give a compound of general formula II-4)

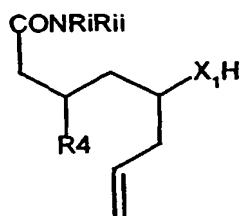


in which R^4 and X_1 have the meaning as defined under formula I,

c) reacting compound II-4) with an amine of general formula II-4a



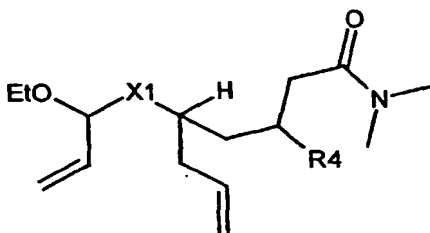
in which R^I and R^{II} independently from each other have the meaning of hydrogen or C_1 - C_6 -alkyl, to give a compound of general formula II-5)



II-5),

in which R^4 and X_1 have the meaning as defined under formula I and R^I and R^{II} have the meaning as defined under formula II-4a,

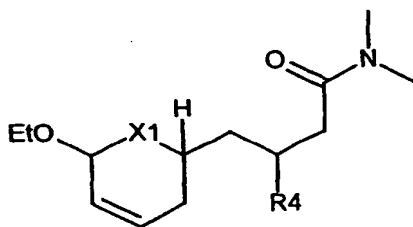
d) reacting compound II-5) in a suitable solvent with a suitable acetal and a suitable hydroxy compound to give a compound of general formula II-6)



II-6),

in which R^4 and X_1 have the meaning as defined under formula I,

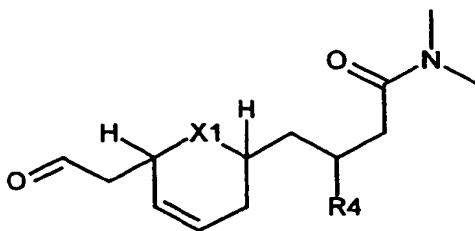
e) deoxygenating compound II-6) in a suitable solvent with a suitable catalyst, to give a compound of general formula II-7)



II-7),

in which R^4 and X_1 have the meaning as defined under formula I,

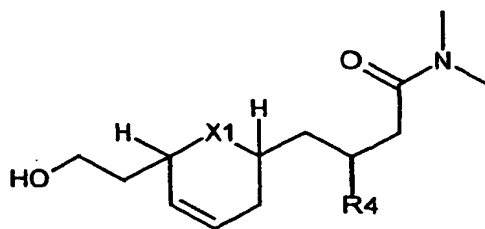
f) reacting compound II-7) with a suitable vinyl ether and a suitable perchlorate in a suitable solvent, to give a compound of general formula II-8)



II-8)

in which R^4 and X_1 have the meaning as defined under formula I,

g) reacting aldehyde compound II-8) with a suitable reductant in a suitable solvent to give an alcohol compound of general formula II-9)



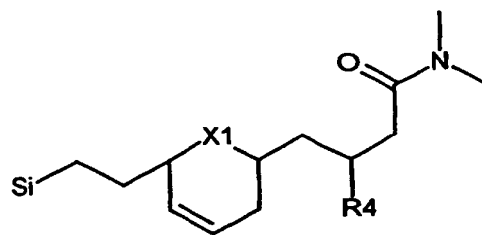
II-9)

in which R^4 and X_1 have the meaning as defined under formula I,

h) reacting a solution of alcohol compound II-9) in a suitable organic base and with a silyl chloride or a triflate (Si) of general formula II-9a)



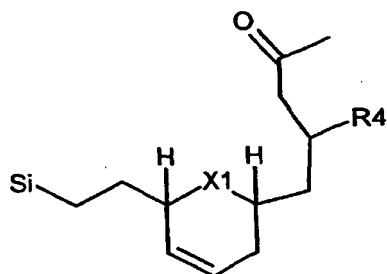
in which R^{21} , R^{22} and R^{23} independently from each other have the meaning of α - or β - C_1 - C_6 -alkyl, to give an amide compound of general formula II-10)



II-10)

in which R^4 and X_1 have the meaning as defined under formula I and Si has the meaning as defined under formula II-9a,

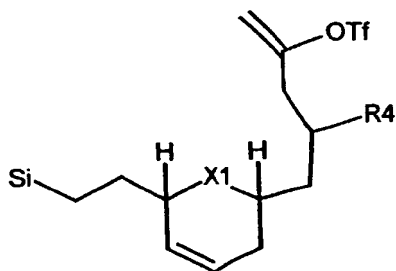
i) reacting amide compound of general formula II-10) with a metal organic compound and in a suitable solvent to give a ketone compound of general formula II-11)



II-11),

in which R^4 and X_1 have the meaning as defined under formula I and Si has the meaning as defined under formula II-9a,

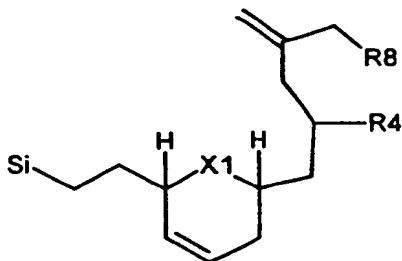
j) reacting the ketone compound II-11) with a suitable strong amide base in a suitable solvent, and accordingly with a suitable acylating agent in a suitable solvent to give an enoltriflate of general formula II-12)



II-12)

in which R^4 and X_1 have the meaning as defined under formula I and Si has the meaning as defined under formula II-9a,

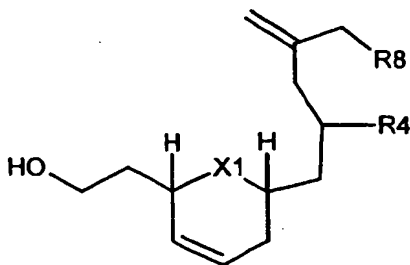
k) reacting enoltriflate compound II-12) with a suitable Pd catalyst and with alkali chloride in a suitable solvent, and accordingly with $TMSCH_2MgCl$ to give compound II-13)



II-13)

in which R^4 and X_1 have the meaning as defined under formula I, R^8 has the meaning as defined under formula II, and Si has the meaning as defined under formula II-9a,

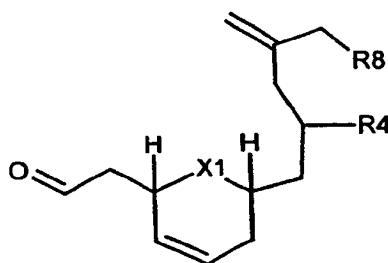
l) reacting compounds of general formula II-13) with a suitable ionic fluoride in a suitable solvent to give compound II-14)



II-14)

in which R^4 and X_1 have the meaning as defined under formula I and R^8 has the meaning as defined under formula II,

m) reacting compound II-14) with a suitable oxidant in a suitable solvent to give an aldehyde compound of general formula II-15)



II-15)

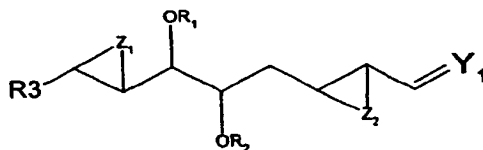
in which R^4 and X_1 have the meaning as defined under formula I and R^8 has the meaning as defined under formula II, and

n) reacting aldehyde compound II-15) with a phosphonyl acetic ester of general formula II-15a)



in which R^x and R^y independently have from each other have the meaning of C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl or phenyl, and with 18-crown-6, and a suitable strong amid base, in a suitable solvent to give the intermediate compound of general formula II).

9. Process for the production of general formula III,

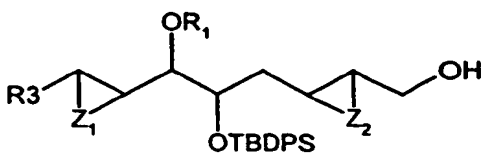


(III),

in which

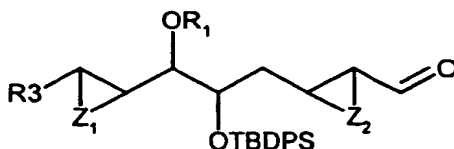
R^1 , R^3 , Z_1 and Z_2 have the meaning defined under formula I, and
 R^2 has the meaning of hydrogen, methylmethylether, paramethoxybenzyl, benzyl, or a protecting group, or a group $-COCH_2B$, wherein
 B has the meaning of the group $-SiR^{10}$, $-SeR^{11}$, $-Se(O)R^{11}$, $-TeR^{11}$, $-PO(OR^{11})_3$ or $-P(O)(OCH_2CR^{10})_2$, in which
 R^{10} has the meaning of alkyl, aryl, alkenyl, or the group $-CF_3$, or $-CH_2OR^{11}$, in which
 R^{11} has the meaning of hydrogen, alkyl, cycloalkyl or aryl, and
 Y_1 has the meaning of oxygen, or an alkyl acetal of the group $-CH(OR^{12})_2$, or a five membered O,O ; N,O ; O,S ; or S,S ; cyclic acetal, or six membered O,O ; N,O ; O,S ; or S,S ; cyclic acetal, and
 R^{12} has the meaning of alkyl, which is characterized in by reacting

o) an alcohol compound of general Formula III-16)



III-16),

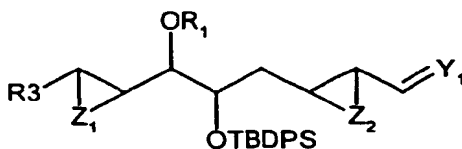
in which R^1 , R^3 , Z_1 and Z_2 have the meaning as defined under general formula I, with a suitable oxidant in a suitable solvent to give an aldehyde compound of general formula III-17)



III-17),

in which R^1 , R^3 , Z_1 and Z_2 have the meaning as defined under general formula I,

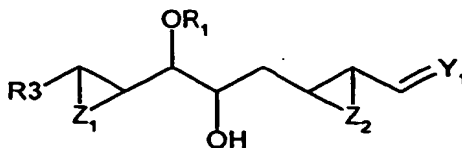
p) reacting a compound of general formula III-17) with an acetal in a suitable solvent to give a compound of general Formula III-18)



III-18),

in which R^1 , R^3 , Z_1 and Z_2 have the meaning as defined under general formula I, and Y_1 has the meaning as defined under formula III,

q) reacting a compound of general formula III-18) with a suitable ionic fluoride in a suitable solvent to an alcohol compound of general formula III-19)



III-19),

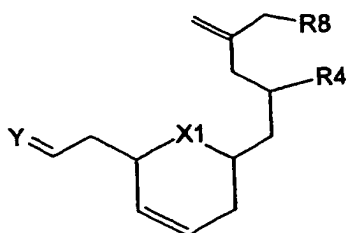
In which R^1 , R^3 , Z_1 and Z_2 have the meaning as defined under general formula I, and Y_1 has the meaning as defined under formula III, and

h) reacting a compound of general formula III-19) with a suitable tertiary amine in a suitable solvent, and accordingly with a solution of a phosphoro acetyl chloride of general formula III-19a



in which R^9 has the meaning of C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl or aryl, in a suitable organic base to give a compound of general formula III.

10. Compounds of general formula II

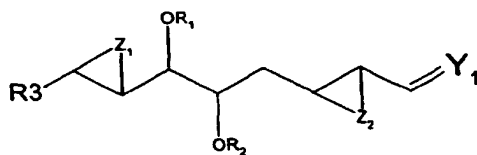


(II),

in which

R^4 and X_1 have the meaning defined above under formula I, and
 R^8 has the meaning of hydrogen, trimethylsilyl, or the group MHal, wherein
M has the meaning of Mg, Li, Ti, Ge or In, and
Y has the meaning of oxygen or the group $=CH(OH)$, (Z) or (E)- $CH-COOH$, (Z) or (E)- $=CH-COOR^9$
or (Z) or (E)- $CHHal$, in which
 R^9 has the meaning of hydrogen, alkyl, cycloalkyl or aryl, as intermediates for the production of compounds of general formula I.

11. Compounds of general formula III



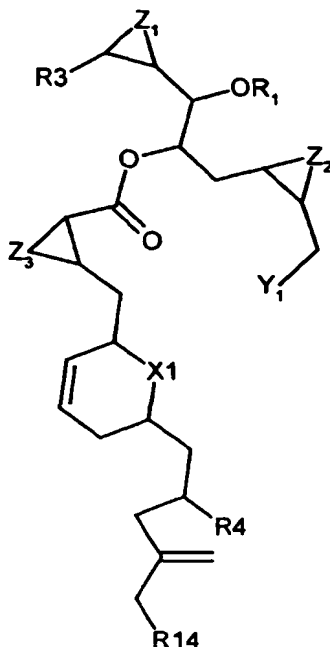
(III),

in which

R^1 , R^3 , Z_1 und Z_2 have the meaning defined above under formula I, and
 R^2 has the meaning of hydrogen, methylmethylether, paramethoxybenzyl, benzyl, or a protecting group, or a group $-COCH_2B$, wherein

B has the meaning of the group $-\text{SiR}^{10}$, $-\text{SeR}^{11}$, $-\text{Se}(\text{O})\text{R}^{11}$, $-\text{TeR}^{11}$, $-\text{PO}(\text{OR}^{11})_3$ or $-\text{P}(\text{O})(\text{OCH}_2\text{CR}^{10})_2$, in which
 R^{10} has the meaning of alkyl, aryl, alkenyl, or the group $-\text{CF}_3$, or $-\text{CH}_2\text{OR}^{11}$, in which
 R^{11} has the meaning of hydrogen, alkyl, cycloalkyl or aryl, and
 Y_1 has the meaning of oxygen, or an alkyl acetal of the group $-\text{CH}(\text{OR}^{12})_2$, or a five membered O,O; N,O; O,S; or S,S; cyclic acetal, or six membered O,O; N,O; O,S; or S,S; cyclic acetal, and
 R^{12} has the meaning of alkyl, as intermediates for the production of compounds of general formula I.

12. Compounds of general formula IV



(IV),

in which

R^1 , R^3 , R^4 , X_1 and Z_1 - Z_3 have the meaning defined above under formula I, and
 Y_1 has the meaning defined above under formula III, and
 R^{14} has the meaning of hydrogen, halogen, trimethylsilyl, or the group MHal, wherein
M has the meaning of Mg, Li, Ti, Ge or In, as intermediates for the production of compounds of general formula I.

13. Use of compounds of general formula I, according to claims 1 to 6, for the treatment of cancer, such as solide tumors and Leukemia, autoimmune diseases, such as psoriasis, alopezia and multiple sklerose, chemotherapeutically induced alopezia and mukositis, cardiovascular diseases, such as stenosis, arteriosclerosis and restenosis, infectious diseases caused by unicellulare parasites, such as trypanosoma, toxoplasma or plasmodium, or nephrological diseases caused by fungi, such as glomerulonephritis, chronical neurodegenerative diseases, such as Huntington's disease, amyotropical lateral sclerose, Parkinson disease, AIDS dementia and Alzheimer's diseases, acute neurodegenerative disease, such as ichemia of the brain and neurotraumata, virale infektions, such as wie

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z. B. Cytomegalus-infectiones, herpes, hepatitis B and C, and HIV diseases.

14. A medicament comprising one or more compounds of general Formula I, according to claim 1 to 6.

5 15. A medicament according to claim 14, together with suitable formulations and vehicles.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 01 25 0331

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (InCL.7)
X	GHOSH, A. K. ET AL: "A macrolactonization-based strategy to obtain microtubule- stabilizing agent (-)-laulimalide" TETRAHEDRON LETT. (2001), 42(20), 3399-3401 XP002189881 * compounds 1, 8,9,15 *	1	C07D493/08 C07D493/18 C07F7/08 C07D309/26 C07F9/655 C07D407/14 //(C07D493/08, 321:00, 311:00), (C07D493/18, 321:00,311:00, 311:00)
X	GHOSH, ARUN K. ET AL: "Total Synthesis of (-)-Laulimalide" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY (2000), 122(44), 11027-11028 , XP002189882 * compounds 1, 19, 20 *	1	
X	WO 01 54689 A (UNIV HAWAII ;UNIV UTAH STATE (US)) 2 August 2001 (2001-08-02) * claim 7, compounds 1-4,6 *	1	
			TECHNICAL FIELDS SEARCHED (InLC1.7)
			C07D C07F
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 11 February 2002	Examiner: Alfaro Faus, I
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

EPO FORM 1503 03/02 (P4/C01)

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 01 25 0331

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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11-02-2002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0154689 A	02-08-2001	AU WO	07-08-2001 02-08-2001

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82